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MALARIA TOXIN AND ACTION OF QUININE IN CLINICAL MALARIA

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Malarial ague has long been known to start simultaneously with the breaking up of the rsoettes. These rosettes liberate besides the young merozoites, hæmozoin pigments. It has been asserted that a toxin is also liberated at the same time; and it is this toxin which gives rise to the clinical symptoms. The nature of this toxin has not yet been determined, but the ague simulates hæmoclastic shock caused by sudden liberation of toxin. Rosenau and others by injecting filtered serum procured during the cold stage have been able to demonstrate its presence (Manson, 1917) However, this particular toxin has not yet been identified.

The hæmozoin pigments are more or less extensively distributed throughout the body. They have been found in the brain and spleen after death from cerebral malaria even when no parasites are present (Viswanathan, 1944). In fact their presence in the body without the parasites is evidence of recent malaria. These granules are found wherever there is any pathological lesion. A lesion is seldom found without the simultaneous existence of these pigments. They are almost co-existent. The degree and extension of pigmentation as well as those of the retrograde changes in the tissues and organs largely depend upon (1) the type of infection, (2) its virulence and (3) the distribution of parasites (Solis-Cohen and Solis-Cohen, 1916). These pigments are distinguishable from those found in other diseases by being both extra and intravascular.

It has been observed that as soon as the hæmozoin pigments are delivered into the liquor sanguinis they are vigorously attacked by the leucocytes which have been found to increase even upto 30,000 in cases of severe infection (Manson, *loc. cit.*) Leucocytosis occurs during paroxysm (Stitt, 1922, Megaw, 1942; Manson-Bahr 1944). These attacks go on every-where in the body in the circulation. spleen, liver, intestine and in fact in every part of the body where the pigments gain access. 'The splenic vein direct from a rich breeding ground contains a large number of hæmozoin-laden leucocytes' (Manson, *loc. cit.*).

These pigments have been regarded by Manson as 'specific products' of the malaria parasites themselves. Banerjee and Bhattacherjee (1913) think that they have a toxic action which produces cloudy swelling and degeneration of the phagocytic cells. Viswanathan (*loc. cit.*) found degeneration of endothelium, the cells of which contained pigments. Haemozoin may act as haemolysin (Manson-Bahr, *loc. cit.*). Stitt (*loc. cit.*) thinks along with Brown that they can also bring about degeneration of the endothelial cells by being taken up by them, with associated capillary haemorrhages. The toxic nature of the pigments may also be deduced from their behaviour prior to the rupture of the red cells. The segmenting schizonts except in cases of *P. ovale* are never big enough to so distend the walls of the cells as to cause their rupture. It seems more probable that the walls get disintegrated through the action of the toxin liberated from the pigments. As the schizonts begin to segment the pigments, which were located mainly at the periphery are discharged from the body of the parasites and occupy a central place surrounded by the segments. In this way it may not act prematurely on the cell walls before the merozoites are fit for liberation. When the merozoites are completely separated from one another toxin from the central accumulation of pigments reaches the wall through the channels running between the segments, and disintegrated. As a result, the merozoits are liberated into the liquor sanguinis.

Leucocytes are considered to be the advance-guards, the first line of defence, against invading forces. From the beginning of invasion, that is, the onset of clinical symptoms these advance-guards attack the hæmozoin pigments to the exclusion of the parasites, which are seldom phagocytosed in the peripheral circulation. Therefore these pigments must be considered to be of primary importance among the invading forces. They persist even after the parasites have disappeared from the body, and disease continues sometimes culminating in the victory of the invaders. Or again the fight continues to such a pitch that the parasites too are attacked in the peripheral circulation as in Das Gupta and Ganguli's case (1944). But here again the schizonts only are phagocytosed to the exclusion of the rings and gametocytes although these latter are much smaller in size. The rational explanation of such a phenomenon lies in the fact that neither the rings nor the gametocytes are of importance, since they are not likely to supply reinforcement soon for a fresh on-slaught, while the natural function of the leucocytes tells them that the schizonts have been bringing fresh contingent for the fight and must be destroyed forth-with without giving the enemy an opportunity to start the fight over again. The rings are hyaline bodies and do not contain pigment until they are fairly developed, neither are they likely to deliver

the pigments, and so do not provoke the leucocytes to action. Similarly, the gametocytes, though they contain a few pigments, are not likely to set them free and cause mischief. Consequently the leucocytes do not take any notice of them. Perhaps herein lies the secret of relapse even in adequately treated cases. It is not the parasites 'lurking in the cells of the reticuloendothelial system' that escape from the action of quinine, since it never had any action on them, but that they being innocent do not stimulate the system to phagocytic action.

Hæmozoin pigments are, therefore, the repository of the toxin which produces pathological changes in the body giving rise to different symptoms in connection with malaria. In the blood it causes destruction of the platelets (Beattie and Dickson, 1921) and the red cells not attributable to the direct action of the parasites. In the spleen it causes thrombosis and focal necrosis (Solis Cohen and Solis-Cohen, *loc. cit.*), liver hepatitis, kidney nephritis, in the brain the varied symptoms according to the particular area affected, and so on. In the vessels it produces pathological changes in the endothelium. Blocking which is considered to be the cause of the cerebral symptoms, is secondary to these degenerative changes as suggested by Viswanathan (*loc. cit.*). Presence of parasites, according to him, inside or outside the cells is immaterial so far as clumping is concerned. Emboli are not found in the hyperpyrexial and hæmorrhagic malaria (Magaw, *loc. cit.*). Sinus thrombosis observed by Viswanathan was probably caused by dangerous fall of blood pressure due to large doses of quinine given intravenously. He did not find the pressure below normal in any of those cases before the commencement of treatment. Unfortunately he does not state the record of pressure during the course of treatment. (Lack (1943) from observation on infected canaries found transient sticking of leucocytes to the endothelial lining of the venules plus evidence of plasma leakage, followed later by clumping of both infected and healthy cells, retardation of the rate of flow and pastelike flow of blood. There must have been some damage of the endothelial cells to account for the sticking of leucocytes. Viswanathan found no evidence of inflammation or necrosis of the brain. 'Intravasculat thrombosis and consequent avascularization' according to him 'is the cause of malarial coma aud death'. Punctiform and other hæmorrhages are probably due to deficiency of blood platelets and damaged endothelial cells.

Divine and Fulton (1941) found the crude hæmozoin pigments to contain only about one-sixth of hæmozoin, which is chemically and spectroscopically indistinguishable from hæmatin, and the rest primarily of 'parasitic protein' which remains undissolved round the pigment granules. This protein envelope seems to be the toxic product of the parasites. It may be that a part of it goes into the

circulation from which Rosenau and others could demonstrate its presence.

Therefore, it is the toxin and not the parasite that is of prime importance. And the pigments are store-houses of this toxin.

Having established this let us see how quinine acts in effecting cure of clinical malaria. Opinion differs regarding its mode of action in malaria. There are several views which may be summarised as (1) direct action on the parasites and (2) indirect action on them through the defensive mechanism of the body. Quinine disintegrates plasmodium *in vitro* in a concentration of 1 in 10,000. But this concentration is never reached in human blood; in fact it never exceeds 1 in 100.000; besides it is rapidly excreted, 90 per cent disappearing within a minute after intravenous injection (Ghosh, 1944); Morgenroth (1918) found the quinine content of the blood to be 1 in 20,000 a few minutes after intravenous injections and 1 in 150,000 after oral administration of therapeutic doses. 'Part of the drug is deposited in the spleen, liver and other organs in an inert form' (Megaw, *loc. cit.*). Maximum concentration is retained in the human blood for only half an hour (Chopra *et al*, 1934). To maintain a steady maximum to be effective, if it is effective at all, against the parasites quinine has to be given every half an hour which is never done. Therefore, owing to low concentration, rapid elimination and partial transformation it cannot act as a parasiticide in the human body. De Sandro (1909) says, 'most of the quinine injected (hypodermically) is found in the spleen where it reaches after an interval of fifty minutes, and it remains there longer than in any other part of the body and can be demonstrated even twenty-four hours after the injection. But in spite of this the parasites accumulate and remain there for a pretty long time and produce relapse. It can neither prevent infection even when the blood is saturated with quinine (Megaw. *loc. cit.*). If quinine had acted as a parasiticide within a minute after an intravenous injection a large number of parasites should have been destroyed. But on the contrary in Gavan Duffy's (1944) case we find he parasites increase by 150 per cent after 16 grains had beenr administered intravenously. Similar increase has also been observed by Chopra and others (1932). Again their rapid destruction should have been followed by aggravation of symptoms owing to sudden liberation of a large amount of toxin. This, however, never occurs. Small doses of quinine quite incapable of destroying parasites, of course, sometimes wake up latent malaria and bring about an ague. But this may be explained by the fact that such doses by causing contraction of the spleen (Cushney, 1936, Ghosh, *loc. cit.*) squeeze out the parasites. I am in the habit of giving parentarally 10 grains of quinine without any stimulant and repeating it after two hours, sometimes 20 grains in a single dose in apparently hopeless cases of

algid or choleraic malaria with dramatic effect. Less than 10 grains in a dose is never given whether the patient is 30 years or 30 days old. The pulse appears at the wrist, temperature rises and evacuation stops within a very short time. Hundreds of such cases have been treated with uniform success. No aggravation of symptoms nor any depression of the cardiovascular system has been noticed. Intramuscular route is, invariably used. Megaw's charts also show how quick and large doses act rapidly in controlling pulse and temperature, while small and leisurely administration delays action sometimes with disastrous result.

To clear up this confusion different workers offer different explanations none of which is, however, convincing. They are (1) that quinine acts on the merozoites but not on the sporozoites; (2) that the mature schizonts but not the rings are affected; (3) that it acts by making the red cells impervious to the merozoites; (4) that it makes the red cells more pervious for the 'all sufficient' serum to act on the parasites within the cells. There is no reason why it could not destroy the sporozoites; both are extra-corpuscular, of the same nature and constitution though different in shape and origin, and both enter the red cells and develop into rings. Similarly, the schizonts and rings are of the same constitution and intracorpuscular. If one is affected why not the other? Again if a coating on the cell wall can prevent entrance why can it not prevent egress as well? In birds inoculated with *P. Gallinaceum* intense quininization could not prevent the merozoites from entering the red cells, neither could it destroy the parasites, which not only survived in liquor sanguinis saturated with quinine but thrived and multiplied as well. The only thing quinine could do was to arrest the growth of intracorpuscular merozoites and keep the erythrocytic schizogony of pigmented form in abeyance so long as quinine is in sufficient concentration in the blood (Adler and Tehernomoretz, 1941, 1943). Some ingredient in liquor sanguinis which is essential to the growth of the parasites is prevented by quinine lrom reaching the intra-corpuscular merozoites. The inevitabls conclusion, therefore, is that quinine does not cure malaria by destroying the parasites.

As regards the second view, phagocytosis of plasmodium undoubtedly occurs both in the peripheral blood as well as in the spleen; but symptoms persist even after complete disappearance of parasites in cases where sufficient quinine has been given for a pretty long time (Viswanathan, *loc. cit.*). Besides prolonged administration of quinine often fails to completely liquidate the parasites and prevent relapse. Moreover, quinine causes a preliminary leucopenia before increasing the leucocytes (Ghosh, *loc. cit.*). Should not therefore, there be an initial aggravation of symptoms? Das Gupta and Ganguli's (*loc. cit*) case put up a heroic fight even in a

starving condition without the aid of quinine before yielding to the enemy. He was a destitute wandering in the streets of Calcutta for a morsel of bread and could not possibly have any quinine which was then selling at one rupee a grain. Even such extreme phagocytosis of parasites as observed by them did not require the help of quinine, neither could it save the patient. So quinine does not cure malaria through phagocytosis.

How then does it act? It acts on the immediate cause of the symptoms thereby relieving them. If toxin is the cause of the symptoms, and there could be no question about it, quinine must act on this toxin. Phagocytes devour the parasites and the pigments, but they cannot destroy the toxin. Quinine does it.

Gupta and Ganguli (1944) found that malaria-infected monkeys tolerated much bigger doses of quinine than noninfected ones. In fact they required higher doses to save themselves. They think that it is absorbed by the parasites thereby relieving the cells of the hosts from its toxic action. If quinine could be absorbed by the parasites how could extra erythrocytic multiplication be possible in the experimental birds of Adler and Tehernomoretz? Where then does this excess quinine go? Howie and Murray-Lyon (1943) observed that in acute subtertian malaria when quinine was not excreted in any urine the condition of the patient remained grave and could only be improved by injecting more quinine intravenously when the drug was detected in the urine as well. Again those who excrete the drug regularly improve rapidly. Ordinarily about one-third of the quinine absorbed appears in the urine (Cushney, *loc. cit.*). Where then does this lost quinine go? What is it required for? Kelsey and Oldham (1943) from studies on quinine oxidase in the tissues found some activity of this enzyme in human liver. During an attack of malaria this activity may be increased and be responsible for the disappearance of the quinine. Gupta and Ganguli (*loc. cit.*) do not consider it likely that the destruction is greatly accelerated by the malarial infection. However, if there is greater destruction or shall we say utilization, there is greater requirement as well, in such cases. The efficiency of the reticulo-endothelial system as measured by the cango-red index is increased in infected monkeys where infection is controlled by quinine and the general condition improved (Gupta and Ganguli, *loc. cit.*). This increased efficiency is probably due to the elimination of the toxin by quinine, since in unchecked malaria this efficiency is diminished, apparently due to the deleterious action of the increasing amount of toxin liberated by the increasing number of parasites on the system. So it is not the parasite that absorbs it, neither does the red cell absorb it, nor is it destroyed by the enzyme merely for the sake of destruction. It renders the toxin innocuous either by absorption or by some delicate chemical reaction with it. The result is that neither quinine nor

the toxin is capable of exerting its individual specific influence on the host. When sufficient quinine is not given to neutralise the whole of the toxin there is no surplus left to be excreted, and the action of the unaffected part of the toxin persists. To be spared for excretion after neutralizing all the toxin, more than sufficient should be administered, when both improvement of clinical condition as well as Tanret reaction are obtained. A third condition may be possible where the quantity of quinine is nothing more nor less than what is absolutely necessary for complete neutralization of the toxin. Here no quinine will be detected in the urine, but the disease will be cured. Since it is impossible to measure the quantity of the toxin it will be a mere chance when this state would be obtained. If the target is not known the bullet will more often than not fall short of the mark or pass beyond it. An ideal dose would be one which leaves a constant trace of quinine in the urine throughout the course of acute attack and gives a faint Tanret reaction. If administration of quinine is stopped before the defensive mechanism of the body is sufficiently developed early relapse is likely: for, we find the dormant merozoites in the red cells developing into schizonts when quinine is eliminated or its concentration in blood is sufficiently lowered (Adler and Tehernomoretz, *loc. cit.*)

The questions that can arise in connection with the action of quinine are, (1) how could infected monkeys tolerate more quinine than what would otherwise have killed them, (2) why quinine sometimes fails to appear in the urine during the course of treatment in acute malaria, (3) why should bigger doses be required by children than their age and weight call for, and (4) why prophylactic use of quinine cannot prevent relapse?

If we accept that quinine acts as an antitoxin all these points can be satisfactorily explained. More quinine is tolerated because the excess is required to neutralize the toxin thereby relieving the cells of the host from its toxic action. Secondly, quinine fails to appear in the urine because of the change in its constitution in the process of neutralization of the toxin. As regards the third point, children have not acquired any immunity which can at least partly control the toxin as happens with the adults; besides the average number of parasites in their blood is about one hundred times that of adult in the same endemic area (Napier, 1943) Hence more quinine is required to neutralize unaided the greater amount of toxin liberated. Fourthly, relapse cannot be prevented even after administration of quinine in prophylactic doses extending over a period of even twelve months; in fact after the stoppage of the prophylaxis the incidence of relapse is actually higher than in those receiving no prophylactic treatment (Field, Niven and Hodgkin, 1937.) This is due to the fact that while quinine could not eradicate or prevent

entrance of parasites, by constant presence in the blood it neutralises the toxin whenever it is liberated by the parasites. Absence of free toxin in the system prevents the growth of immunity in the host. Consequently when the drug is withdrawn relapse occurs uncontrolled by any immunity. So from whatever angle it is seen the only possible conclusion is that quinine acts as an antitoxin.

SUMMARY AND CONCLUSION

Pathology of malaria and its relationship with the hæmozoin pigments are discussed. Hæmozoin pigments are the repository of the toxin which produces the morbid changes giving rise to the varied symptoms of clinical malaria.

Fallacies of the current views on the action of quinine in malaria are pointed out and a new theory, that quinine acts as an antitoxin by combining with the toxin whether by absorption or by some other delicate chemical reaction is enunciated.

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PROGRESS OF SURGERY IN THE PROVINCE OF MADRAS*

T. S. SHASTRY, LT-COL., I.M.S.

As a little boy I happened to see a Hospital Assistant pass a metallic catheter in a struggling adult in my neighbour's house and draw some bloody urine. It was in Kottajatam in the Nellore district. This simply horrified me and for many years haunted me.

As a school-boy I used to attend the post-mortem work of the Local Fund Hospital Assistant in Giddalore, Kurnool District, during my summer vacation. This led me to think on the beauties of the structure and functions of the internal organs of the human body.

My father was a patient suffering from a chronic disease and often used to ask me to take up the study of Medicine.

Dr. Pattabhi Seetharamiah was the first Andhra M.B. and C.M. (1907)—a pionner for us, Andhras, and furnished a stimulating example.

I saw terrible sight one forenoon in May 1908 while travelling in a bullock cart on the Bunder-Bezwada road. A boy of 10 years fell vertically down on the road in front of me from the top of the tree about 50 feet high. His right arm snapped and two broken pieces shot out.

* Address delivered at the Surgical Section of the South India Provincial Medical Conference, Trichinopoly, Oct., 1945.

All these interested me greatly and quickened my desire to join the Medical College. I joined it in July, 1908.

In those times the state of surgery was thus :—

Abscesses, carbuncles, superficial tumours, amputations, piles, fissures, fractures, hydroceles, urethral strictures and hernias—whoever did those operations became famous as a great surgeon. Hernia was a serious operation! Removal of elephantoid scrotum was a big undertaking! Removal of cataractous lens was a wonder! Forceps delivery and completing an abortion formed the obstetrical surgery of those days! D & C was the stock-in-trade in gynaecology. Chloroform was the only anæsthetic and was usually administered by compounders. Most of the surgical work was confined to district hospitals, and that was the monopoly of the I.M.S. officers.

Dr. Nedungadi was the first Indian to be appointed as a Surgeon in the Madras General Hospital in 1916. That was a land mark indeed! Dr. Rangachari was the first Indian Surgeon who performed really first class surgery. No part of the body escaped his knife. His work was good both in quality and quantity.

Among independent practitioners, none had a nursing home with theatre, staff and equipment. Dr. T. M. Nair did some E.N.T. operations but he was not noted as much of a surgeon. Dr. Varadapra Naidu did some carbuncles, having worked with Major Smith who resigned from the I.M.S. Dr. Naidu was much in demand in the districts. Generally, people from all part of the Province resorted to the General Hospital, Madras. Surgery by independent practitioners was an uncommon phenomenon in those days. Thus arose the general notion that no Indian was competent to do decent surgery and that surgery was really a monopoly of the British I.M.S. officer.

In 1912, one evening in May, I met at Bhimadole (West Godavari District) the huge, uneducated son of an old-time zemindar who was a famous hunter. He openly told me not to attempt to do surgery, as no Indian was ever competent temperamentally to do good surgery, and he went on praising Major Niblock of the Madras General Hospital for his skill for operating an abscess on his leg! This stung me to the quick, and I determined to break this tradition. So, when I got the chance, being surgically inclined by nature, I devoted myself to surgical work. I have ample reason to be gratified with my choice.

The first Great War was a windfall indeed to us Indians who were keen on doing high class surgery. Nearly all the I.M.S. officers were then pulled away to war-duty. Some of the assistant surgeons had to be given charge of district hospitals and teaching jobs in medical colleges and schools. This opportunity proved their intellectual calibre, professional skill and efficiency of hospital management. Many of them proved to be good and great surgeons

Drs. Chandrasekhara Mudaliar, Ganpat Rao, Madhava Rao, Halge, Krishniah, Padmanabha Sarma, V. Krishna Murthy, Trasi, R. Ganapathy Iyer, Nedungadi, Ranga Chari, Lakshmanswami Mudaliar (now Sir) created the surgical era in 1915.

Of all these, the most out-standing surgeon was undoubtedly the late Dr. S Ranga Chari who practically lived in his Rolls Royce—an 'ever ready' surgeon, noted for his popularity, quickness, studied reserve, and a spirit of universal sympathy and service—all this success came to him without any foreign training thus showing what a mere M.B. & C.M., could do. In any other country he would have surely been honoured by his Alma Mater with the Honorary Degree of M.S. or D.Sc. But the University of Madras had no imagination, nor a sense of magnanimity or properiety to honour one of its own brilliant alumni. The grateful public, however, installed a full-sized statue of Dr Ranga Chari appropriately at the very entrance to the General Hospital.

Among the independent practitioners in Madras, Dr. E. V. Srinivasan led the way in eye surgery, while Dr. T. S. S. Rajan became quite an institution in Trichinopoly Dr. Ramasubramaniam came into fame in Madura quite early in his career. Then came the honorary system. The honorary surgeons made quite a good place for themselves in some hospitals.

Now-a-days surgical skill of high order is available in many towns. Many surgeons have equipped themselves for advanced surgery by training in foreign countries. Nobody now dreams of preferring a British to an Indian surgeon unless it be Dr. Somervell of Himalayan fame—but that is not because he is British but because he is a great surgeon, and a humanitarian like the late Rev. C. F. Andrews of blessed memory—in fact he is a citizen of the World.

Thus the old fiction that high class surgery is the monopoly of the British race has been exploded by Rangachari and others. Today many Europeans—both civil and military, go to Col. Pandalai, Dr. Mangesha Rao and others.

Starting of nursing homes was the next development. I remember Dr. Lakshmipathy's Nursing Home in Madras 1910. But it was only in name and soon disappeared. Dr. Rajan's was really the first nursing home started, maintained and well-equipped, and he has done good work indeed in this line. Then came Dr. Rangachari's surgical hospital in Madras. He did most of his first class operative work there, and trained some juniors who, in turn, have opened nursing homes which are all flourishing. Dr. Ramasubramaniam started his nursing home in Madura and is doing very good work. Col. Pandalai has built a palatial private hospital for surgery—this is easily the best of its kind in our presidency. Dr. Sundaravadanam followed suit in Madras. Captain Sunkavalli has a good one at

Bezwada. Dr. Raju and his partner have an ambitious nursing home in Palakol, West Godavari. Dr. Subramaniam's is a good one at Karaikudi with a good record of work. Trichinopoly itself has three other nursing homes—Dr. Raghavan's Dr. Kalamagham's and Dr. Balu's.

During the Second World War, now happily ended, many young and aspiring surgeons served in the Defence Forces in all the different sectors. They have done splendid work, acquired experience, attained high military rank and very good name. Here I must mention with sincere pleasure my own junior officers, Major V. Srinivasan and Lt. K. Parthasarthy who served on my staff when I was Commading the 39th. Indian General Hospital in Sudan and in Egypt in 1941 and 1942. The doctors of this Province, I am glad to say, have volunteered in largest numbers, gained a lot of military and surgical experience and international contacts in the various theatres of war and added to the reputation of the Indian medical profession; of them we are justly proud.

I hope that when these surgeons return to civil side they will be given suitable jobs in the hospitals in the metropolis and other towns. Those who cannot get such jobs ought to be encouraged to open and maintain their own surgical homes with the aid of demobilised nurses—if possible on co-operative basis, with pathological laboratory x-rays, etc.

The large quantities of surgical and medical equipment which the American and British find to be surplus when their military hospitals are closed should be secured by the Government for Government, local fund, missionary and other hospitals for the surgical use. Our medical colleges have, of course, better surgical staff than before, and I am sure that they will produce better results if given the required equipment. For obvious reasons I am not detailing the name of their staff. Perhaps the best agency for these surplus stores to be made available to surgeons is the Government Medical Stores which may open a Sales Department—I have taken this from Dr. M. V. Natesan of Madura.

The crying need today is more Medical Colleges. We have one at Vizag, two at Madras, one at Vellore, and one is under design for Madura. But what about the northern districts? I hope that the policy of neglect of the Andhra area will not be continued hereafter. I expect Guntur will get a Medical College started in July 1946. The required staff, if there is paucity, can be provided for by employing for some time some of the retired surgeons and physicians who are keen and fit to take up this work. Meanwhile the required number of staff must be selected and sent out by the Government to the U.S.A. and trained adequately in all the subjects and employed on suitable terms in these new Medical Colleges.

In seleting these and other personnel and specially in dealing with the proper employment of war-returned medical and nursing personnel, the Government will be well advised to take the advice of the Indian Medical Association by asking the I.M.A. to send its representatives to the selection committees.

One warning is needed now. Enough experimentation has been done and enough mischief, injury and discontent and even frustration have resulted from the implantation of stern communalism in the matter of admissions into the Medical Colleges. It is time that a just policy is adopted.

One very good development is the starting and growth of the Association of surgeons of Indian in 1938 as a result of the initiative of Col. Pandalai. It is flourishing. I hope this and other specialist' Associations—which by the way had their-birth-place in Madras, (at least, most of them) agree and arrange to hold their sessions jointly with the Indian Medical Association hereafter, and thus make themselves useful to the general body of the profession. In this connection I greatly appreciate the efforts of Dr. Jivraj N. Mehta.

Are we fully satisfied with the present state of our surgery? I believe special attention must be given to the surgery of the brain, surgery of the chest, reconstructional surgery and surgical research. Adequate surgical training is necessary. Surgical workshops for artificial limbs etc., and experimental laboratories are to be established for each teaching hospital. Vienna is no longer the Mecca or Kāshi of modern surgery, but the Mayo clinic and others of its kind will give all facilities to us in the U.S.A.

Fellow members, there is a great future and scope for surgery in our country if all the available material be properly utilised and if we serve the people with integrity, sympathy and devotion.

Medical News & Notes.

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STERILITY AND PREVENTION OF CONCEPTION*

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INTRODUCTION

This evening, I shall place before you my observations on a considerable number of patients that have sought advice for the relief of sterility or for the prevention of conception. I have selected two different year-groups: One group includes cases seen in the period of five years beginning from June, 1933 and ending in May, 1938, and the other period beginning in June, 1940 and ending in May, 1945. In the first period, I have records of 1,786 cases who came under my care. Of these 196 persons were anxious to conceive, and there were 476 others who had conceived and wanted to be so treated that they would never more concieve. There were a few in this group who were pregnant at the time of the visit. They wanted to be relieved of the pregnancy and to be sterilised at the same time. In the second period, I have records of 5,893 cases. Of these 1,560 cases came in for the treatment of sterility, and 77 pregnant patients wanted the pregnancy to be terminated and to be sterilised at the same time, 192 pregnant patients wanted to be relieved of unwanted or undesirable pregnancies, and lastly, 76 patients who had been pregnant, but desired to be sterilised. Throughout my career I have received only three requests from husbands to get them sterilised. I have never yet been requested to have a temporary sterilisation.

STERILITY

The cases for sterility will now be discussed. Indian patients frequently come with a combination of the three common complaints of dysmenorrhoea, scant periods and sterility and this last is mentioned by the way. Dyspareunia as a symptom is seldom mentioned unless enquired about. It is very rare for an Indian girl to seek relief of sterility as the only symptom after a few years of marriage. Most Europeans and Anglo-Indians on the other hand seek medical advice if they do not get pregnant within a year at

* A paper read under the auspices of the Bengal Obstetric and Gynaecological Society and the Calcutta Medical Club, September 7, 1945.

the latest after marriage has been consummated. To this general statement a remark should be made about a new group of cases where pregnancy is deliberately prevented in the first few years of married life, and subsequently when pregnancy does not appear medical advice is sought. In this group, I have frequently come across cases where few initial pregnancies have been done away with by questionable means by unscrupulous persons. The genital apparatus has already been damaged and they would not function when desired to do so.

Treatment :—Here are few observations on the treatment. Male sterility is often lost sight of. Azoospermia and oligospermia are by no means rare in husbands reliably free of venereal affections. Functional irregularities in connection with insemination do not appear to be frequent at all. Most husbands complain of frigidity on the part of the wives. This complaint can in most cases be traced to indifferent "sex-play" on the husband's side. Disparity in age or consanguinity on the partners do not play any prominent part. Marriages between members of different races are usually fruitful. For the examination of the semen, the condom specimen is most suitable for practical purposes. Examination from the vaginal pool or from cervix is practicable in only a few cases. Biopsy of testicular tissue, however important it may be from investigation point of view, is not a practical proposition in most cases. Masturbation specimens are small in quantity and are thick in consistency.

Next comes the patient. Recently married patients (by this I mean patients within first three years of marriage after sixteen years of age with normally developed but acutely anteverted and anteflexed uterus) are most satisfactory cases to treat. I have done dilatation and cruettage on a number of such cases with uniformly good result. The next group of successful cases have been those with rigid hymens and absolute dyspareunia as the guiding symptom. Well planned Fenton's operation and dilatation of the cervical canal have been successful in most cases. Patients with retroverted uteruses have also been a problem. I am still doubtful as to what should be the best treatment for all cases.

No generalisations can be made about surgical interferences designed to make insemination feasible and easy. Under this heading are included such operations as perineorrhaphies, trachelorrhaphies and other plastic operations on the vagina. I have done nineteen salphingostomy operations. I am sorry to say I cannot claim a single success out of the series. Artificial insemination from the vaginal pool has been done in three cases. One out of this has definitely been successful.

Investigation: Rubin's original test has been carried out in fifty-four cases without any untoward result. The modified Bonny's test is now being carried out without any bad effect. It has frequently happened that patients with negative tests have often been pregnant. Hystero-salpingographies have a very limited usefulness in everyday practice.

A considerable number of Indian patients come for treatment of sterility ten or more years after marriage. These patients do not usually have any other symptoms and this might account for their late appearance. The husband very often is desirous of getting another wife. Before he does so he thinks it expedient to have the wife treated. Unfortunately, very little can be done for these patients. In a few of such cases I have detected azoospermia in the husband. The poor wife has thus been indirectly spared from the inconveniences associated with the sharing of the husband's love with a co-wife.

A few words about the medicinal treatment: The hormones are evidently indicated for the treatment of menstrual irregularities. Their usefulness in increasing libido in the female is very limited. I have bitter experience of the careless use of such drugs as damiana and yobimbine. Vitamin-E has frequently been used along with other remedies. I am not in a position to pass any opinion about the special efficacy of this particular treatment. I have no experience about the usefulness of such general measures as mud baths, electrical massages and so forth.

The types of women :—Broadly speaking, I divide young women who come for the treatment of sterility from an appearance point of view under three groups:—(1) The average young woman with normal build and secondary sexual characteristics. (2) The corpulent bulky girl with profuse growth of hair in the extremeties and perhaps under the umbilicus or on the face. (3) The thin wiry individual with poor development of secondary sexual characteristics. In type-1 sterility is often due to causes outside the essential organs of reproduction. In type-2 sterility is present for a considerable number of years after marriage, but once conception starts it goes on regularly for years together. Type-3 cases if not treated soon after marriage never conceive later on in life.

Prevention of Birth

Now I come to the second part of my talk this evening, *viz.*, the prevention of births. I do not propose to express my views on contraceptives. I shall discuss my views on deliberate abortions, by which I mean instrumental and/or medicinal methods of terminating early pregnancies and on means of preventing pregnancies by surgical operations on the genetal apparatus.

Drugs like quinine, alcohol, oestrogenic hormones and other medicines are often resorted to in order to produce abortions True in some cases they succeed. Inconveniences and risks following surgical operations are no doubt avoided. But in spite of these

apparent advantages I have always deprecated such measures in all cases. The greatest disadvantage is that the uterus is most frequently incompletely evacuated, not to speak of the great number of cases where these measures either completely fail or by producing some amount of vaginal bleeding give the patient a false and temporary satisfaction about the termination of pregnancy.

I have come across many cases when people who know their job have introduced a sound to disturb the products of conception in the uterus, hoping that the uterine contractions will subsequently expell them. This practice I have never subscribed. I need not explain my reasons. Introduction of tents and/or plugging the cervical canal with gauze however carefully done is a practice which I do not uphold. Sepsis does follow in most cases. My plan in all cases is to deliberately dilate the cervical canal and complete the evacuation with my fingers and sponge holding forceps. Tents are used in selected cases. The choice of an anaesthetic is important. I recommend intravenous anaesthesia with barbiturates, preceded by morphine and atropine. My experience of vaginal hysterotomy is limited. I have always looked upon it as a messy operation. I have seen a few patients months and years after the operation has been done by experts. I cannot say I can honestly praise the operation.

The commonest surgical device adopted to procure sterilisation in the female is the ligation of the tubes. This can be done both by the abdominal and vaginal routes. I have done this operation both ways. The best results so far as sterilisation goes are obtained by the abdominal operation. The complications are numerous after abdominal sections. Failures are more frequent after vaginal operations, although complications are usually few. The operation is however not one which should be taken light-heartedly. Apart from the discussion of its justification from the point of view of all religions and from ethnological point and even allowing for the ordinary complications associated with surgical procedures, this operation has got far reaching affections in the woman's life. I have known people who have been insane as an indirect effect of this operation. Menstrual troubles are too frequent. I have done at least dozen hysterectomies on such patients for fibriods. There are scores of women who suffer from various troubles the causes of which can be traced to this operation.

(*Calcutta Medical Journal Oct. 1945.*)

THE MODERN TREATMENT OF GONORRHOEA IN THE MALE.

The sulphonamides now chiefly used in the treatment of gonorrhoea in the male are sulphathiazole and sulphadiazine. . . . There seems to be little difference between the efficacy of sulphathiazole and sulphadia-zine. . . . .

The greatest certainty of cure follows the establishment and maintenance of an effective blood level of the drug, and this may be attained in ambulant patients by giving 5 gm. daily in divided amounts for 5 days. There is no advantage in continuing sulphonamide therapy, for the cure rate is not increased and there is a marked increase in toxic effects. Shorter courses do not usually give such a high percentage of cure as the 5-day course, unless a more intensive dosage such as 6 to 7 gm daily is adopted, and this is often inadvisable in ambulant patients. Sub-optimal dosage leads to immediate failure to cure, as shown by persistence of clinical signs and the development of sulphonamide-resistant strains of the gonococcus, making subsequent treatment more difficult. The daily dosage of 5 gm. should be given in 3 amounts, spaced 8 hours apart, *e. g.* 1.5 gm. after breakfast, 1.5 gm. about 8 hours later, and 2 gm. before going to bed.

During sulphonamide therapy there is a two-fold action, inhibition of bacterial growth by the drug and destruction of the damaged organisms by phagocytosis or bacteriolysis. Any factor tending to inhibit this mechanism such as under dosage of the drug, consumption of even small quantities of alchol, or local tissue trauma, may lead to chemotherapeutic failure. In successful cases their is rapid clinical improvement, within 24 hours, the urethral discharge decreases, and within 48 to 72 hours it is absent. The urinary haze soon clears and the bacteriological improvement is parallel. After 24 hours gonococci cannot be detected in urethral smears, though there is a varying amount of pus which gradually diminishes and is absent after the third day.

The cessation of signs and symptoms and negative bacteriological findings, however, do not indicate certain cure. Observation and repeated tests are necessary for at least 3 months.

From 50 to 60 per cent of cases treated with sulphonamides require no further treatment than the first course, and are shown by a subsequent follow-up to be cured. In the early days of sulphonamide therapy the cure rate was claimed to be from 80 to 95 per cent following a single course, but in the years since then the rate has shown a progressive fall. It has been shown in vito that gonococci become tolerant to sulphonamides when exposed to increasing concentrations, and there is also a host factor to be taken into consideration.

Failure of sulphonamide therapy may be immediate and partial or complete, or it may be indicated by frank clinical relapse or the onset of complications, usually within a month of cessation of treatment and apparent cure.

In such cases, to continue the sulphonamide therapy is useless and may lead to sensitisation of the patient or to a blood dyscrasia. A careful clinical examination and urine-glass test should be carried out to determine whether the persistent infection is limited to the anterior urethra, or also involves the posterior urethra.

Sulphonamides are also frequently ineffective in cases where there are shut-off or intermittently draining foci of infection.

Various methods have been advocated for the treatment of these cases of primary sulphonamide failure, namely local irrigation and administration of gonococcal vaccine followed by a second course. of chemotherapy ; fever therapy, and penicillin therapy.

While there is still considerable diversity of opinion as to whether local treatment is necessary or not during the acute stages it is agreed that such treatment is indicated in relapsing or refractory cases. The antiseptics generally used are potassium permanganate 1:10000 to 1:8000, albargin 1:800, and mercury oxycyanide 1:10000. Since the posterior urethra is involved in the large majority of cases reporting for treatment posterior irrigation is the method of choice.

Ten to 20 per cent of the cases of partial failure following sulphonamide therapy will clean up after local irrigations for a few days.

Better results, however, are obtained with a combination of local treatment and vaccines. An initial dose of 0.1 to 0 2 cc. of a detoxicated polyvalent gonococcal vaccino (50,000 million organisms per c.c.) is followed by gradually increasing dosage, twice a week, to a maximum of 1 c c., and the subcutaneous route should be used. In in-patients the intravenous route may be preferred, in which case the initial dose is 0.05 c.c. This combined treatment is followed by marked clinical improvement and in many cases by the complete cessation of the urethral discharge and urinary haze, but it is advisable to give a second course of sulphonamide therapy and preferably to use a different drug from that employed for the first course. Cases responding to the second course of sulphonamides should be followed up in the same way as the primarily successful patients.

Failure of the second course of sulphonamides to cure is frequently associated with closed or intermittently draining foci of infection in the glandular structures of the anterior urethra, or in the prostate or vesicles. Careful examination of the lower urinary tract should be carried out, and treatment by prostatic massage

twice a week, with subsequent urethro-vesical larvae, should be instituted if infection is foudd in the prostate and seminal vesicles.

Involvement of the glandular structures of the anterior urethra requires treatment by instrumentation, followed by urethral lavage

After local treatment has continued for 10 to 21 days, and according to the rapidity of the clinical progress, a third course of sulphonamide therapy should be given and the majority of refractory cases will then respond.

Fever therapy has gained a place in treatment of sulphonamide-resistant gonorrhoea, although it is now being largely displaced again by penicillin. It may be applied after failure of the first course of sulphonamides, concurrently with the second course, or later. The fever may be obtained by physical means, using a Ket. tering hypertherm, or inductotherm, or by the intravenous injection of TAB or B. coli vaccine. The initial dose of TAB is 25 million organisms, and of B. coli 50 million, subsequent dosage being graduated to produce fever of stisfactory height and duration. In cases where a satisfactory degree of fever does not develop, a second injection of about half the dosage may be given 2 to 5 hours after the first. If bacterial fever therapy is employed, a futher course of sulphonamide therapy should be given after its termination.

The introduction of penicillin, however, has gradually improved the outlook in sulphonamide-resistant gonorrhoea, as well as providing a rapidly effective means of curing recent infections. A total dosage of 150,000 units given in 5 equal amounts of 30,000 units 3-hourly is curative in nearly all cases.

After the first injection gonococci disappear from the discharge in 2 to 4 hours, the urethral discharge rapidly becomes scanty and mucoid, and is often absent after 12 to 24 hours. Subsequent observation shows the patient to be cured. Sometimes, however, mucoid urethral discharge may persist for several days, though it contains no pus cells or gonococci and clears up spontaneously.

Possible failure of penicillin therapy is suggested by the persistence of a marked urethral discharge, though these cases respond satisfactorily to a further administration of 100,000 to 150,000 units on the subsequent day.

While the cure rate of recent or complicated gonorrhoea treated with penicillin is nearly 100 per cent, failures are to be expected by analogy with other forms of chemotherapy. Such cases have so far been cured by repeated course, of penicillin, though local therapy, vaccines and fever may be needed in the future.

In considering the duration of follow-up after successful penicillin treatment of gonorrhoea, the effect of this drug on spirochaetes must not be overlooked. A dosage of 100,000 units of the drug is not curative for syphilis, but is sufficient to heal a primary sore or mask its development. In a case recently seen by the

author the primary sore with satellite adenitis occurred 3½ months after the successful penicillin treatment of the gonorrhoea contracted at the same time. Subsequent observation of penicillin treated cases should follow the lines suggested for sulphonamide treated patients, but it should include a final serological test at the fifth or sixth month, (McLachlan, Abstracted from the Practitioner Vol. 154, No. 5, May 1945, Page 295).

THE MODERN TREATMENT OF GONORRHOEA IN THE FEMALE.

The introduction of chemotherapy has produced great changes in the treatment of gonorrhoea in the female, but it is important that the old measures of giving at least 6 pints of bland fluid a day and alkaline diuretics, etc should not be abandoned.

Sulphathiazole is the drug suggested, the initial dose being 2 gm. and the subsequent doses 1 gm. four-hourly for 48 hours and then six-hourly until a total of 30 gm. has been taken. A mixture containing 30 grains of potassium citrate per dose is given 3 times a day.

If there is marked intolerance the drug should be stopped, and a white cell count made, and if this is satisfactory a 20 gm. course of sulphadiazine is started. Smears should be taken from the cervix and urethra immediately after the end of treatment and repeated at weekly intervals for a month, then post-menstrual smears should be taken for at least 3 months.

In vulvo-vaginitis of childhood sulphathiazole can be given in doses appropriate to the child's age, and stilboestrol in doses of 1 mgm. 3 times a day for 21 days.

Treatment of gonorrhoea in pregnancy is on the same lines as in non-pregnant patients, but the insufflation of sulphanilamide into the vagina is avoided as instances of air embolism have been recorded during this procedure in pregnant women. Tests of cure are rigidly applied before discharging the patient and extra precautions should be observed during the confinement.

The patient may be seen for the first time because of an abscess of Bartholin's gland, and the possible presence of the gonococcus as an underlying cause must not be overlooked. The patient should be thoroughly examined under anaesthesia and smears and material for culture should be obtained from the urethra and cervix and pus from the abscess should also be cultured. The abscess should be laid open and packed with flavine gauze and a full course of sulphathiazole given.

In salpingitis the patient should be kept in Fowler's position, antiphlogistine fomentations are applied to the abdomen, and hot vaginal douches given to alleviate the pain. The sulphathiazole is administered in full doses and morphine may be needed. Fluids can be given by mouth, unless there is vomiting, in which case an intravenous drip should be employed, with glucose saline to a total of 6 pints in 24 hours, and sodium sulphathiazole can be given in the drip.

Gonococcal proctitis is treated with chemotherapy and relief of local symptoms is obtained by rectal wash-outs of lead and opium lotion (O. Lloyd, Abstracted from the Practitioner, Vol. 154, No. 5 May 1945, Page 302).

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Extracts.

MANAGEMENT OF THE ACUTE HEAD INJURY.

This war has so far yielded a much higher proportion of closed head injuries than was expected, and as a consequence emphasis has been placed on the medical aspects of their management. In the field the neurosurgeon is faced with the immediate repair of soft tissue.

An apparently trivial head injury may soon cease to be trivial if great surgical care is not taken from the beginning. When all the immediate steps have been taken there is a period of anxious watching, especially if the patient is in coma, and it is then that the medical aspect of the injury becomes as much a concern of the surgeon as of the neurologist.

Symonds and Russel have shown that the results of conservative treatment of acute head injuries may be excellent. But this does not mean that the physician should remain idle. After attention to the immediate surgical condition his purpose should be to establish a base line from which he can measure any changes in the patient's condition. The depth of unconsciousness and the behaviour of the patient should be accurately assessed, and abnormal signs should be observed by routine exmination.

A lumbar puncture should usually be performed, not just because blood may be found or because the pressure may be raised, but because an increase in the amount of blood or of pressure may indicate the progress of a complication such as an increasing intracerebral, subdural, or extradural hæmorrhage.

X-ray examination of a skull may indicate a depressed fracture, or one involving sinuses or the middle meningeal region which may call for surgical intervention. The problem is one of diagnosis rather than of treatment.

If the watchful clinician finds any signs of deterioration of patient's condition, he should hand over the case to experienced neurosurgeon for exploration. If no signs of deterioration are found, he should treat him by giving him every chance to survive the period of maximal cerebal commotion. He should be kept quiet by such drugs as chloral or intramuscular paraldehyde, should receive nourishing fluids by mouth unless coma is so deep as to cause the risk of aspiration, and should get all the nursing that will conserve his powers of recovery.

The patient should not be restrained, and the confused, mildly resistive patient is better sitting in an armchair than being unnecessarily restrained in bed. It may not seem satisfactory merely to remain watchful in the acute stages of head injury, but the results justify the self-discipline which such an attitude requires.

—*British Medical Journal* 1944 April 22, p. 593.

FOOD AND THE HEALING OF WOUNDS.

Previous good health and nutrition are great assets to a wounded man.

People who have sustained fractures, invariably lose nitrogen and phosphorus. If these are supplied in the nutrition, the union of fracture is not retarded. Of course, it is not proved that, the union is hastened by giving these lost nitrogen and phosphorous.

In extensive burns, there is an enormous loss of body proteins at the site of the injury, so much so that even in multiple transfusion the serum proteins may become dangerously low.

Sepsis, malaise and toxæmia all interfere with appetite, and may render the task of feeding the patient so difficult that a vicious circle establishes itself. It was with the idea of breaking this circle that the administration of intravenous aminoacids was first taken up in America Hypoproteinæmia should be relieved whenever it is encountered in a surgical patient. Free use of plasma transfusions and the introduction of amino-acid mixtures intravenously is recommended. Casein hydrolysates have usually been employed for this purpose.

The vitamins must not be forgotten. Even slight deficiency of vitamin C, interferes with the normal process of bone repair. The same is true for skin wounds. Saturation of vitamin C in body does not hurry the repair of wounds. But Boston workers suggest, however, that maximal saturation of the tissues with vitamin C may increase their resistance to infection, and infection is of course a potent cause of reduced tensil strength in wounds. The ideal should be to give them a full mixed diet high in calorie value and in protein and vitamin content, supplementing it to meet special circumstance. Where this is not practicable, we must use our best endeavours to see they do not fall short in protein and vitamin C.

Lancet (1944 June 3, p. 727.

MECHANISM OF INFLAMMATION.

Menkin has introduced four new concepts as regards inflammation, two of which take concrete form in substances liberated in areas of inflammation and having specific effects.

These are leukotaxine, a polypeptide which has been isolated in crystalline form from inflammatory exudates, and is responsible for increased capillary permeability and chemostatic effect of

leucocytes, and the leucocytosis promoting factor, a pseudoglobulin which acts on the bone marrow.

His other new concepts are the effects of pH in regulating cytology and the fibrin barrier, which walls off the affected area and constitutes "the primary and basic mechanism of fixation" of localization of the process.

Inflammation is essentially the same, however produced—by microbic invasion, or physical and chemical agencies.

To this Menkin adds another mechanism, in the form of specific substance, which is responsible for local injury and for fever and other more distant effects. This injury factor, which he calls "necrosin" is contained in the euglobin fraction of inflammatory exudates, from which it can be extracted by prolonged dialysis.

Necrosin can also be extracted from the blood serum of dog a day after inducing pleural effusion with temperature. That it is in fact absorbed from inflammed area and exerts distant effects is shown by the consequences of injecting it intravenously in normal animals. These are sharp fever, and a leucopenia succeeded by a leucocytosis, degenerative changes in kindneys and liver.

The first two substances—leucotaxine and leucocytosis-promoting factor—produced by the body in the inflammatory exudates are useful to the bodies.

British Medical Journal (1944) May 20, p. 694.

STUDIES ON MERCURIAL DIURESIS SUDDEN DEATH FOLLOWING INTRAVENOUS INJECTION

BY I. F. VOLINI et al

Mercury is a protoplasmic poison. The use of organic mercurials as diuretic has become very extensive in the therapy of edema. The diuretic action represents the very early toxic action of mercury on the renal tubules. Inorganic ionizable compounds of mercury are more potent in diuretic action than nonionizable organic mercurials. Mercury ion released in small amounts from the organic mercurials is responsible for the diuretic action. Mercury has been known for its diuretic activity since the time of Paracelsus and was a constituent of the Guy's Hospital pill, which contained calomel, squill aud digitalis.

Several workers reported sudden death from the intravonous injection of organic mercurials.

Experiments on dogs showed that intravenous injection of mercurials produced death by ventricular fibriliation. The relative toxicity of the various organic mercurial diuretics was studied. De Graff and Lehman showed that Esidrone was the most toxic of the mercurials, followed in order by salyrgan, mercurin, mercupurin with salyrgan theophylline, the least toxic. They demonstrated that the added theophylline radical played no role in the causation of sudden death. Previous treatment by various drugs such as ammonium chloride, phenobarbital, intravenous aminophylline and digitalis had no effect on the lethal action of mercurials. They also observed that dilution of the drugs is of little value in preventing sudden death. Nor were they able to prove that the rate or speed of the intravenous injection contributed to the toxicity and fatal terminatlon.

The death is caused by the direct action of these drugs on the heart. Ventricular fibrillation or respiratory failure secondary to cardiac action is the usual manifestation and cause of death. Ventricular tachycardia frequently precedes the onset of venticular fibrillation.

No reports of sudden deaths have been found from deep intramuscular injection or the rectal or oral use of these substances but the diuretic effect is unsatisfactory in these cases. The authors reported sudden death in three cases. Electrocardio graphic studies are available in 2 patients. Both patients showed the development of ventricular fibrillation following the drug.

Intravenous injection of mercurials should not be discontinued, but the realization of danger of their use must be ever present. This is in addition to four such possible other dangers as the dehydration syndrome, the depletion of chlorides, the disturbance of the electrolytic balance and the sudden mobilization of large amounts of digitalis from the edema fluid.

The Journal of American Medical Association,
5 May, 1945, (12—17)

OXALURIA IN BRITISH TROOPS IN INDIA

BY J. M. BLACK M.B., F.R.C.S.E.

Oxaluria was found to be very common in urological cases in British troops in India. Out of Seventy seven urological cases 43 cases or 55 per cent were due to oxaluria.

SYMPTOMS

The symptoms of oxaluria in 43 cases were :—

(1) Renal colic in 20 cases
(2) Haematuria 15 cases
(3) Epididymitis and cystitis 8 cases.

RENAL COLIC

Out of 20 cases of oxaluria with renal colic only five had urinary symptoms—frequency or strangury. One patient complained of severe pain in right iliac fossa without urinary symptoms and so was diagnosed a case of perforation.

HAEMATURIA

The urine in all 15 cases contained red cells and calcium oxalate crystals. In 4 cases haematuria was painless, in other 4 with dysuria, in others 7 in number there was Renal or uretric pain.

OXALURIA

With Epididymitis. 8 cases. Five of the eight cases had some dysuria before the oneset of pain and swelling of the epididymitis. Pulse and temperature were normal. The condition is one of irritative epididymitis due to oxaluria and direct spread down the vas.

TREATMENT

Avoid sorrel, rhubarb, and asparagus and exess of chocolate, tomatoes, strong tea. Hot weather causing loss of body fliud by sweating and concentration of the urine and inadequate fliud intake and presence of oxalate forming food in the diet are the chief causes. Fluid at least 8 pints a day are taken to eliminate the crystals. Ammonuim chloride is given to prevent phosphate deposit so calculus formation. Alkalies by mouth do not help its prevention.

British Medical Journal,
28 April, 1945, (590—592)

INTRAVENOUS ARSENIC IN TREATMENT OF ANGINOUS FORMS OF GLANDULAR FEVER

By K. S. SMITH, M.D., F.R.C.P., & T. H. SHAW, M.B.

Severe inflammation of the tonsils and fauces in glandular fever may cause serious illness which may even threaten life. The treatmeet of glandular fever is solely palliative but in serious anginous type arsenic not only produces conspicuous and rapid improvement but may prove to be life saving.

The throat lesions of the anginous type of glandular fever may be among the most servere that can be encountered. Not only may there be massive edema but there may be extensive ulceration causing considerable bleeding. Bronchopneumonia may develop and bring about fatal issue. Severe dysphagia often occurs, militating against the full fluid intake so desirable in acute febrile illnesses.

Local treatment is of no avail in such cases. Intravenous injection of neoarsphenamine 0.15—0.45 g acts in a dramatic manner. The authors treated six patients suffering from anginous glandular fever. Speedy and conspicuous benefit was obtained.

British Medical Journal
28 April, 1945, (528—524)

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TREATMENT OF MALARIA IN GENERAL PRACTICE*

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The first sentence in the excellent treatise on tropical medicine by Admiral Stitt and Colonel Strong goes to say that "from the standpoint of prevalence malaria appears to be the most important of all diseases in the world to-day." Although adequate morbidity and mortality statistics regarding malaria are not available, yet Paul Russel says that no disease has or has had through centuries a more profound influence on World Health than malaria.

A competent observer has said that the eradication of malaria in India would in a single generation convert it from a most indigent into a most prosperous country in the world. Sinton, the former Director of the Malarial Survey of India, states. "There is little doubt that malaria is responsible for at least two million deaths each year in India." Paul Russell puts down the incidence of malaria at about three hundred millions a year in the world, of which one-third or about one hundred million cases occur in India alone.

In reply to a question in the Central Assembly Mr. J.D. Tyson revealed that malaria alone took a toll of more than nine million (9,079,418) lives in British India from 1938 to 1943 of which Bengal claims more than eighteen lacs during the year 1943 and more than twelve lacs during the year 1944, up to September 30,1944. Various relief workers of Bengal have estimated that about thirty millions out of Bengal's sixty millions were stricken with malaria in the year 1944.

Yet, far from distributing quinine free of charge the Government sold quinine to people at double the rate of its cost per pound even in pre-war days. During the ravaging epidemic of the last year although the Minister of Health announced, early in January 1944, that enough quinine to treat ten million patients was released by the Government—the price of quinine soared and ranged between Rs. 400 and Rs. 800 in the black market, and yet the stuff available was not genuine and trustworthy.

Recently mepacrine has been made available as a substitute for quinine, but unfortunately it has not as yet been received with the confidence it deserves—partly for want of adequate information of

*A paper read before the Calcutta branch of the Indian Medical Association July 19, 1945.

its properties beforehand and partly on account of the suspicion with which a new remedy, particularly when it is sought to be forced, in order to replace a tried and popular remedy such as quinine, is looked upon by the public. It has to be popularised amongst the practitioners who minister to the needs of the multitude of rural population.

If the country has to be rid of this terrible scourage the problem has to be dealtwith in its preventive as well as its curative aspects.

A tremendous amount of research, both chemical, pharmacological and clinical, is going on at the present moment to find out an ideal anti-malaria chemotherapeutic agent, a *therapia magna sterilizans*, which will have none of the demerits and deficiencies of quinine, plasmochin and mepacrine. The need for it will be realised when it is recalled that none of these drugs will prevent malaria, or cure it with certainty or will effectively prevent a relapse after an apparent cure. Not one of them is dependable for the control of malaria on a mass scale

It is not proposed to go into the problem of prevention of malaria, nor even into the treatment of malaria in extenso but to convey to the reader certain informations with regard to its treatment which are interesting and useful to practitioners in the tropics, particularly at a time, when we have been deprived of about 90 per cent of our supply of quinine after the fall of Java, and a large part of the residual 10 per cent is consumed by military operations, conducted in countries where malaria is endemic or hyperendemic.

In view of the very limited supply of quinine available, parsimony has to be practised so that the drug may not be wasted, but may be used in its optimum dose, when and where necessary. Totaquina is a useful substitute. It contains not less than 7 per cent and not more than 12 per cent of anyhydrous quinine and a total of not less than 70 per cent but not more than 80 per cent of anyhydrous crystallizable cinchona alkaloids. The dose is 10 gr., thrice daily for seven days. Cinchona febrifuge is inferior to totaquina, and is used in the same dose for the same period.

PRINCIPLES OF TREATMENT OF MALARIA.

The treatment of malaria may be considered from six points of view :—

1. *True causal prophylaxis*, i.e. administration of a drug that will destroy the sporozoites injected by the mosquito before they enter the red cell and commence their intra-corporeal cycle Unfortunately no known drug can achieve this.

2. *Clinical prophylaxis*, i.e. administration of a drug that will check the multiplication of the parasites and prevent an infected person from developing an attack of clinical malaria, without necessarily destroying all the parasites. This can be effected by administering quinine, six grains a day, during the whole of the

malaria season and preferably continued at least for about four weeks after the close of the malaria season or after the subject leaves the infected region. Atebrin, 0·1 gm , twice daily may be used for the same purpose for two days in the week with an interval of two or three days. This treatment is appropriately described as suppressive treatment.

3. Treatment of clinical attack by the administration of atebrin or quinine to be described later (treatment for *clinical remission*).

4. Treatment to prevent or reduce the chances of relapse by treatment with atebrin, quinine and plasmochin in various combinations (*treatment of latent infection*).

5. Prevention of the *formation of gametocytes*: No drug is available for this purpose, but once they are formed they can be effectively destroyed.

6. *Destroying the gametocytes* for general prophylaxis: Quinine and atebrin have effect on the gametocytes of *Pl. vivax* (benign tertian) and *Pl. malaria*, but plasmoquin is the only drug which has a killing effect on those of all the varieties particularly the crescents of *Pl. falciparum* (malignant tertian).

After the introduction of *artificial malaria therapy* for the treatment of general paresis by Wagner Jauregg in 1917 it was observed that quinine given prophylactically was effective against inoculation with the blood of patients but not against mosquito-induced infection—the conclusion being that *quinine did not affect the sporozoites but the trophozoites* only. Hence quinine did not really prevent infection but it only suppressed clinical manifestation of the disease.

SYNTHETIC ANTI-MALARIALS.

The Elberfield Laboratories of I.G. Farbenindustrie synthesized plasmochin in 1924, since then variously called as plasmoquine, praequine, pamaquin etc. Atabrine dihydrochloride is an acridine dye developed in 1930 by Kikuth and Schulemann with the collaboration of Mietsch and Mauss, and is variously called as atebrine, mepacrine hydrochloride, quinacrine, acriquine. Extensive chemical pharmacological and clinical studies have demonstrated that the American product quinacrine hydrochloride (U.S.P. XII) and the British product mepacrine have effects in all respects identical with those of the German product atebrine. The French product quinacrine, the U.S.S.R. product acriquine and the Italian product crinodora (first called palusan) are also identical.

[A compound prepared at the Haffkine Institute, Bombay, and at first named Haffkinine and later acriquine and another prepared by the Bengal Immunity and named as alecrine appear also to be identical.]

The introduction of synthetic drugs in addition to quinine has given us certain advantages in the combined therapy over the old

quinine method. The period of treatment is greatly shortened, the cost is cheaper, and relapses are less common. Besides mepacrine was the only life-saving drug during the acute scarcity of quinine, and is the only dependable substitute for it. Mepacrine is the schizonticidal agent, and is therefore given first to deal with the acute attack. Plasmoquin is the gametocidal agent, and is therefore administered later to prevent relapse. They are not to be given concurrently.

MEPACRINE.

The solubility of mepacrine in water is about 1 per cent and the solution gives a neutral reaction. Being a dye substance it may after absorption give rise to a harmless yellow pigmentation of the skin. When it is desired to administer it parenterally in cases of coma, in very young children and in severe vomiting, mepacrine soluble (the dimethane sulphonate of the base) is employed. Mepacrine is not considered to be a general poison, which quinine is, since it does not decrease the oxygen consumption of isolated brain and testicular tissue.

Mepacrine acts on the asexual forms of all the malarial parasites, as well as on the gametocytes in *Pl. vivax* (B.T.) and *Pl. malariae* forms. But, its action on the schizonts of *Pl. falciparum* (M.T.) is perhaps its outstanding property.

Toxic Symptoms: Mepacrine is of low toxicity and is quite safe for mass administration. In susceptible individuals, towards the end of the course the drug may give rise to: (*a*) gastro-intestinal disturbances, e.g. epigastric pain, vomiting diarrhoea; (*b*) symptoms from the central nervous system such as cephalalgia, mental depression, delirium, psychoses and convulsions. In some cases symptoms of excitement comparable to those of alcohol have been noticed; (*c*) collapse and death. I have read of two cases of death (reported by Fied, Niven and Hodgking)—who died during prophylactic administration of atebrine and both showed fatty degeneration of liver– one was alcoholic and the other was anaemic, who had received some other quack treatment also before his death.

These toxic symptoms occur more frequently when the treatment is unduly prolonged, when the doses are excessive or when atebrin musonate by injection is followed by the oral use of atebrin. These symptoms may be prevented in most cases by giving the drug after food along with alkalies, sweetened drinks and copious fluid. They are never serious and almost invariably disappear soon if the drug is discontinued. The report on Malaria Therapeutic Trial, Assam carried out by Lt.-Col. J. M. Rogan also confirms the above view. He treated with mepacrine 1,000 cases among Indian troops whose average body-weight was 119 lbs. It was found that mental symptoms were not in direct relation to the dose of mepacrine and it was stressed that equal weight should be attached to the *Pl. falciparum* (M. T.) infection which prevailed in the majority of cases.

The standard treatment now adopted for *British troops* in the India Command is as follows:—

1st day: 9 tablets; 2nd day: 6 tablets; 3rd. to 7th. days: 3 tablets daily=a total of 30 tablets.

For Indian trooops:—

1st. day: 6 tablets, 2nd. day: 6 tablets; 3rd. to 7th. day: 3 tablets daily=a total of 27 tablets.

Absorption and elimination: Mepacrine is rapidly absorbed and evenly distributed over the body tissues, 2½ hrs. later the concentration is relatively greater in liver, gall bladder and intestines. It takes about a week or ten days to disappear from all organs, but traces of it may be found up to nine weeks after the end of the treatment. This is due to the slow excretion and cumulative effect of the drug. Mepacrine in full course should not, therefore, be repeated within a month's time, if there is a relapse after one course of treatment, such relapse being treated with quinine if available, or with mepacrine in moderate doses.

Other Effects of mepacrince are :—

Blood: Mepacrine is selectively absorbed by the erythrocytes and possibly by the parasites. It cannot be completely extracted from the blood even with alcohol.

Blood pressure: This is lowered, due to vasodilation. It causes dilatation of the coronary vessels as observed in the isolated heart of the monkey. It may cause inconsiderable rhythmic disturbances, while large doses may lead to heart-bloc, ventricular flutter and fibrillation. Because of these effects it should be combined with ½ c.c. of 1 : 1000 solution of adrenalin, if it is to be injected intravenously.

In the *isolated uterus* of pigs, rabbits and cats: concentration as 1: 200,000 has a stimulating effect upon muscular tone and frequency of contraction, whereas higher concentration of 1 : 20,000 has the opposite effect. The use of mepacrine in pregnancy is not only not contraindicated in the dose in which it is given, but is used in preference to quinine.

Liver: Some observes compared the similarity of liver damage caused by cinchophen to that sometime observed with mepacrine. In dogs the cholic acid output was impaired, pointing to the possible hepato-toxic action of the during. But, as stated already, the yellow discolouration of the skin, after the administration of mepacrine is due to deposit of the dye stuff in the skin and has nothing to do with icterus or jaundice.

Test: A very simple test for detection of mepacrine in urine is given by Peter. The urine is made alkaline and mepacrine is extracted with ether. The ether is evaporated and the residue is dissolved in concentrated sulphuric acid. A yellow colour and fluorescence shows up the presence of mepacrine.

Therapeutic effect: Speaking generally mepacrine and quinine have the same effect in the treatment of malarial infection though not always in the same degree. Degenerative and destructive influence of mepacrine upon young ring forms of *Pl. falciparum* (M.T.) on the cytoplasm as well as the chromatin was studied by Hewitt and Richardson.

De Court stressed the dysgenic action of mepacrine. He believes that the asexual reproduction and gamete formation of schizonts became almost entirely lost. The fourth report of the Malaria Commission of the League of Nations stated that the therapeutic daily dose of 0·3 gm. of mepacrine acted somewhat more rapidly on the trophozoites of *Pl. vivax* (B.T.) than did quinine in the dose of 1 gm. The trophozoites disappeared after the second or third dose of mepacrine and the parasiticidal action lasted longer after treatment with mepacrine than with quinine. The same is believed to be true with the trophozoities of *Pl. falciparum* (M,T.) and *Pl. malariae*. However the relative values of mepacrine and quinine

did not seem to be clearly established to the Commission. It expressed itself very cautiously regarding a possible slight superiority of mepacrine over quinine in the action on the gametocytes of *Pl. vivax* (B.T.) and *Pl malariae*. As far as the gametocytes of *Pl. falciparum* (M.T.) were concerned both quinine and mepacrine were powerless.

As regards prevention of relapse, mepacrine is superior to quinine, the relative frequency being about 8 per cent with the former against 50 per cent with the latter.

Later observers are generally agreed that mepacrine is definitely superior to quinine in the treatment of acute attacks of *Pl. falciparum* (M.T.) because of its more rapid action on the trophozoites. A daily dose of 0·3 gm. of mepacrine causes disappearance of *Pl. falciparum* (M.T) trophozoites after four days in 90 per cent cases. Whereas quinine in dose of 20 grs. per day will achieve the same result in five to seven days. But on some strains of *Pl. falciparum* (M T.) quinine appears to be more effective than mepacrine. Mepacrine therefore is preferred in *Pl. falciparum* (M.T.) cases in patients sensitive to quinine, or in whom there has been a relapse after quinine, particularly in pregnant women, and in patients suffering from black-water fever.

As the course is shorter and the cost much cheaper it is the drug of choice in the treatment of rural hyperendemic areas where people are invariably poor and death is due to *Pl. falciparum* (M.T.) infections.

Although the parasites disappear more rapidly with mepacrine, the reduction in the size of the spleen is more slow than with quinine, which latter has perhaps a more rapid effect on the fever.

PLASMOCHIN SERIES.

Plasmochin, plasmoquin, praequine or pamaquin is a salt of a synthetic quinoline derivative (I C.I.) obtained in 1944. Praequine (M & B) is avilable in 0·01 gm. tablet form. It is a tasteless. pale yellow, granular powder relatively insoluble in water but readily soluble in alcohol. It has the power of destroying the gametocytes of all types of malaria parasites and specially those of *Pl. falciparum* (M.T.) which are not acted upon by quinine or atebrin and is therefore particularly of value as a prophylactic against the disease and helps to control the spread of malaria.

In *Pl. vivax* (B.T.) and *Pl. malariae* infections, in combination with quinine it reduces the relapse rate from 50 per cent (with quinine alone) to about 20 per cent.

It is also effective in the actue febrile stage, but for its toxicity its use is superseded by quinine end atebrine, as the margin of safety between the therapeutic and toxic doses is very narrow.

It can also be used in the treatment of pregnant women.

It is not used alone but in associaiion with quinine or atebrine It has no destructive action on the asexual parasites of *Pl. falci) parum* (M.T.) and has got a slight effect on those of *Pl vivax* (B.T. and *Pl. malariae*, compared to that of quinine or atebrin *It can be used concurrently with quinine but not with atebrine.*

Plasmocide, Rhodoquine or Fourneau 710 is also a valuable product of the same series. It only lacks a $CHCH_3$ group in the side chain.

Toxic symptoms of plasmochin are epigastric pain, anorexia, nausea, vomiting, diarrhoea, dizziness, cyanosis due to methaemoglobinaemia. It interferes with the new formation of hæmoglobin after prolonged administration. Jaundice due to toxic hepatitis occurs in more than 3 per cent cases. Methæmoglobinuria and transient albuminuria, coma, collapse and even death.

Dose :—1 tablet 0·01 gm. (3/20 gr.). three times daily, after meals for five to seven days. Debilitated patients should receive only two doses daily.

B. P. dose :—1/3 to 3/5 gr. (0·02 to 0·04 gm.) *i.e.*, 2 to 4 tablets daily. Its use is relegated to the after treatment of malaria, when the acute stage has been treated by quinine or mepacrine. Toxic symptoms are treated with injections of glucose and adrenaline.

Cilional or Certuna is also a quinoline product of the same series introduced by Schulemann. It is more potent than plasmochin in its action on the exflagellation of the male gametocytes of *Pl falciparum* (M.T.). It has one-third the toxicity ot plasmochin. *Dose* :—0.03. gm. thrice daily, for four days, *i.* e. a total does of 12 tablets or 0·36 grm. is sufficient to remove the crescents from the peripheral blood and is well tolerated. Atebrin or quinine is given during the early stage to treat the asexual forms as in the case of plasmochin.

Tebetren is another drug being an acridine dye combined with quinine and cholic acid. It has a rapid action and little or no toxic effects. It destroys *Pl vivax* (B.T,) and *Pl falciparum* (M.T.) forms and inhibits the formation of gametocytes. Each tablet is of 3 grs., and is given every 4 hours for 30 deses for one course. Intramuscular and intravenous injection of 3 to 6 grs. may be given in suitable cases for two or three days.

INDIGENOUS DRUGS

Of other drugs mention may be made of the indigenous drug—Alstonia Scholaris or *chhatim*, It was assayed in 1942 by Mukerji, Ghosh and Siddons, and an alkaloid 'ditamine' was found to be the active principle of the bark. It was tried in *Pl Knowelsi* of monkeys and in naturally occurring human malaria but there was *little or no demonstrable action* and was *not recommended* as a substitute for quinine or other cinchona alkaloids.

TREATMENT PLAN OF MALARIA

The ideal for a complete treatment of malaria is a judicious combination of quinine, mepacrine and plasmochin in order to have the full effects of these anti-malarial specifics, both on the asexual and the sexual stages of the parasite, so that malaria may be cured clinically and its relapse and propagation may be forestalled prophilactically. For this reason they have been combined in the undermentioned courses recommended by the American Sub-Committee on Tropical Diseases of the National Research Council. The alternatives are suggested to suit the exigencies of the time to meet the nonavailability of drugs under war conditions. Regarding "suppressive treatment" atabrine is the only drug mentioned in these recommendations which are being quoted in extenso :—

(1) *Combined 'Q.A.P.' treatment* (method of choice) :—

(*a*) Totaquina or quinine sulphate, 10 grs., thrice daily, after meals for two or three days, or until pyrexia is controlled.

Then give :

(*b*) Atabrine, 0·1 grm. (1½ grains), thrice daily, after meals for five days. Then after two days without anti-malarial medication give :

(c) Plasmochin, 0·01 gm. (3/20 gr.,) thrice daily, after meals for five days, except for debilitated patients who should receive only two doses daily. (Discontinue if toxic symptoms occur. *Never give atebrine and plasmochin concurrently*).

(2) *Atabrine-Plasmochin treatment* (may be used for simple *Pl. vivax* infections and in other infections when no totaquina or quinine is available) :—

(*a*) Atabrine, as above for seven days. Then after two days without anti-malarial medication give plasmochin 0.01 grm, three times daily for five days, as above-

(3) *Totaquina or Quinine-plasmochin treatment method* (when no atabrine is available) :—

(*a*) Totaquina or quinine sulphate, as above, for seven days during the last five of which, accompany each dose of totaquina or quinine with plasmochin 0.01 grm., thrice daily,

(4) *Suppressive treatment* :—

Atabrine, 0.1 gm. (1½ grains), twice daily, after food on two days a week, allowing a two or three days interval between the days of medication.

This outline of routine therapy was followed by a note of caution : "It was the consensus of this Sub-Committee that until we have had more experience with the use of atabrine it should be uesd only under the guidance of a physician or public health officer."

German observers, on the other hand, who had experience with malaria in 1941 were positive in stating that gastro-intestinal troubles occurred chiefly in cases where plasmochin had been

combined with atabrine. Among the "great number of malaria patients of 1941 treated predominently with atabrine" hardly any serious gastro-intestinal complaints which might influence prophylaxis or therapy were encountered." Even in cases of malaria combined with acute gastro-enteritis or dysentery, the troubles were not such as to interfere with treatment. Extensive trial in India also confirms the view that it is quite safe for mass administration.

The combined "Q. A. P." course was given as the method of choice by the Surgeon General. U. S Army in his circular No. 135 dated October 21, 1942.

Parenteral administration was suggested in the following cases :—

Malaria with coma : Quinine dihydrochloride, gr, 10 in not less than 200 c.c. sterile normal saline with ½ to 1 c.c. of 1 in 1,000 adrenalin solution intravenously, very slowly, say in twenty minutes, may be repeated after eight hours, but not more than twice in twenty-four hours, till oral medication is possible. We give the same in 25 c.c. of 5 per cent glucose solution intravenously in about the same time.

Malaria with vomiting: Either 1 0 gm. of quinine dihydrochloride in 10 c c. of sterile normal saline with urethane intramuscularly into the gluteal region, repeated if necessary in eight hours, or 0.2 gm. of atabrine dihydrochloride in 5 c.c. of sterile normal saline injected intramuscularly, if quinine is not available.

For the *treatment of children:* Euquinine or ethylcarbonate of quinine is tasteless and particularly suitable in children.

[It is important to note this drug is converted into ordinary bitter quinine if it is mixed with honey or any acid stuff such as orange juice etc]

If euquinine is not available, a very useful method is to emulsify ordinary quinine sulphate with liquid paraffin or olive oil, 4 grains per drachm, and to have the requisite dose floated on a little milk sweetened with chocolate. In *children below three years*, quinine should not be parenterally. If necessary atabrine soluble should be used instead, for quinine is much more irritant and causes necrosis of tissues almost directly. Besides Fletcher has shown that intramuscular quinine is absorbed more slowly than after oral administration.

Quinine : Recent literature contains relatively few additional data on the clinical effects of quinine, most studies being concerned with an evaluation of synthetic drugs as compared with quinine. Mayer Tanrets' reagent is a valuable aid for the qualitative and quantitative of quinine from the patient's urine.

Lay Press In our country, it is rather unfortunate that toxic effects of mepacrine, supposed and real, including cases of mental excitement and aberration, have been advertised in an exaggerated

form in the lay press. This is not justified, for it creates a very grave suspicion against a very valuable drug which if not used by the doctors or refused by the patients will result in loss of lives which might have been otherwise saved, particularly in view of the acute scarcity of quinine. As pointed out already these toxic symptoms are infrequent if administered after food and in proper dosage. They are short-lived and pass off completely after the administration of alkalies, bromides, glucose, sweet drink and copious fiuid. Mepacrine after one course should not be repeated in a month's time owing to its delayed elimination. Mepacrine is superior to quinine in the treatment of *Pl. falciparum* (M. T.) infection and it is the latter which is responsible for the devastating mortality in India and elsewhere.

There is a prejudice among certain sections of the people against the administration of fluid to women suffering from malaria after child birth lest the body of the mother fails to 'dry'. This must be guarded against, by suitable words of assurance from the doctor.

In severe cases of cerebral malaria along with intravenous injection of quinine, lumbar puncture should also be performed and 20 c. c. of cerebro-spinal fiuid withdrawn and carefully examined for meningococci, so that proper line of treatment may be adopted, for, a practitioner during epidemics of malaria sometimes suffers from a mental obsession and sees nothing but malaria in every bush. Similar precaution is necessary in the treatment of algid malaria by examining blood and stool at the same time. As to the dosage of mepacrine recent observes are inclining more to the higher side. The previous discussion about 15 or 16 tablets for a complete course for adults weighing about 120 lb. is now veering round an upper scale of 21 to 24 tablets in 5 to 7 days. Of course this may be useful as a general guide. For an average Indian patient 16 tablets dosage is usually enough for a course. But it may be reduced or exceeded according to the body-weight of the patient, his tolerance and above all, the discretion of the physician.

It is not wise to be guided by hide-bound dogmas in therapeutics for that would only make one a parrot or a technician and not a physician, who has constantly to make use of his own power of observation and draw his own conclusion.

In conclusion, it is only proper to point out that the treatment of malaria is by personal medication. Parenteral route is only necessary in exceptional cases for specific indication. It is always the total quantity of specific drug that matters. It is not a fact that quinine or atebrine, given parenterally, is equivalent to a greater quantity of these drugs given perorally.

NON-SPECIFIC PROTEIN THERAPY IN IMMUNITY.

BY DR. A. CHARAN.

Of the various methods employed in immunising the person against infections of known and unknown origin Non-Specific protein Therapy holds an important place specially in latter cases. Chronic infections and condition of *uncertain etiology* respond favourably to this therapy.

The *modus operandi* of these non-specific protein antigens is a controversial question and to give one's verdict is treading on an uncertain path. But the favoured view is that these like specific antigens act by increasing the opsonic Index.

The latter term is used to denote the concentration of opsonin in tissue fluids, a substance which facilitates the phagocytic activity of the various body cells *i.e*, (1) Leucocytes or Polymorphonuclear cells of the blood, known as Microphages. (2) *Histiocytes or Endothelial cell.* Macrophages of Metchinkoff.

As to the source and nature of *opsonin*, not much can be said with impunity.

Common protein antigen is used in non-specific immunisation. Various non-specific antigens have been used from time to time, and practically every soluble protein has some antigenic properties, some of the toxic glycosides and lipoids have shown similar properties. The commoner ones in use are

(1) Milk proteins. (2) T. A. B. vaccine. (3) Protozoal vaccine. (4) Albu-lipins. Lipoids from bile and various bacterial suspensions etc. in combination with albuminoids.

Index of Immunity. The manifestations of the defensive reaction provoked by the par-enteral administration of foreign proteins is a variable phenomenon. But index of immunity is gauged by (1) degree of phagocytosis induced over and above that of the patient :—

Phagocytosis determines the course of any infection for the greater the phagocytosis the shorter is the course and milder is the infection—

Phagocytosis as mentioned above is brought about by the various body defensive cells.

(2) Temperature and Leucocytosis induced after the stimulation likewise indicate the success as upto a certain limit the higher the tempo and leucocytosis the better are the results.

Factors determining the Severity of reaction. Immunity reactions produced by stimulation with a protein antigen vary greatly and range from an imperceptible one to that of extreme shock characterised by high pyrexia, vasomotor and other constitutional disturbances the important factors determining the severity are—

I. Nature of antigenic substance injected. II. Dosage III. Physical state of patient IV. Mode of parenteral administration. V. Number of previous injections. One cannot have the exact idea of the subject without going into detail of each factor and makes it necessary.

I. *Nature of antigenic substances.* (Reaction to primary stimulus).

Nature of antigenic non-specific protein commonly used like others specific antigens is assessed in terms of (*i*) Leucocytic response, (*ii*) constitutional symptoms and (*iii*) the period of immunity conferred *i.e.* duration of action o the antigen (*iv*) negative phase or phase of leucopenia and under these headings the consideration of following is made.

Milk Proteins. Gives maximum Leucocytic responsitic after primary stimulation (first injection) constitutional symptoms are less marked than with T. A. B. vaccine. The period of Immunity as gauged by leucocytosis is of 24-48 hours after which period secondary stimulation shows little rise in leucocytic count and activity of the cells. Negative phase of leucopaenia lasts for 1-2 hours.

T. A. B. vaccine :—Gives rise to a lesser degree ef leucocytosis in proportion to extremely marked general and local symptoms. The duration of negative phase of leucopaenia following immediately after injection is of 2 hours and as usual is followed by positive phase of Leucocytosis. The immunity is short lived and shows no enhancement at subsequent stimulation.

Protozoal Vaccines:—Leucocytic response is next best to milk protein, constitutional symptoms are less than both mentioned above. Negative phase of leucopaenia lasts 1 hour and the immunity response as gauged by leucocytic count increases at subsequent stimulation in proper doses and spacing *i.e.*, the count increases at subsequent injections and so does the activity of leucocytes.

Albu-lipins:—Give the least marked general and focal reactions and leucocytic count initially is low although it increases as subsequent stimulation giving rise to a progressively increasing immunity, the higher limit of the leucocytic increase being not yet ascertained.

B. Coli Vaccine :—Gives stronger reaction than either T. A. B. vaccine or Albu-lipins.

Although the activities of the few above mentioned common protein antigens has been generalised, it can, by no certainty, be emphasised that these are always the reactions obtained. The fallacies crop by way of (*a*) variation in nature of substance and (*b*) variability of preparations used *e.g.* milk preparations of different manufacturers have seldom given a concordant result.

Considering the various non-specific proteins mentioned above one can say that after a parenteral administration of these an immediate leucopenia develops lasting 1—2 hours and is followed by a leucocytosis maximum in 8—12 hours consisting chiefly of granular cells of polymorphonuclear type having greater phagocytic activity than the lymphocytes which are supposed to be less active probably because they contain less of mobile cytoplasm (Chomler).

The purpose of active immunisation by specific or non-specific antigens is to adjust and time the different doses, so that the negative phase is prevented and a high positive phase of immunity is maintained. It would be worthwhile mentioning here that although negative phase and shock is much dreaded in practice variations of dose and spacing do not show the reaction, in such proportions.

Reactions to Secondary stimuli of Protein antigens :— The reactions of haemopoitic system to secondary stimulation (repeated injection) of various protein antigens mentioned have shown that the phenomenon of leucocytosis (evidence of haemopotic response) is most marked after milk protein and least after T. A. B. vaccine and Albulipin—while in latter two cases the leucocytic activity is maintained—while age, sex and constitution of the individual and nature of the disease play their respective roles.

It has been observed that application of secondary stimuli injudiciously has resulted in partial or even total suppression of the initial reaction and many cases have resulted in troublesome side reactions.—(Ghosh).

II. *Dosage* :—In administering a course of non-specific medication for non-specific immunisation one must be conscious of its limitations.—(*i*) that below a certain mimnial threshold value there is no reaction and (*ii*) above this the immunity response varies with the dose administered till a point is reached at which further increase in doses results in little or no increase in antibody formation.

In considering the dose and its adjustment the clinician has to consider the—

(*a*) Physical condition of the patient. (*b*) nature of antigen· and (*c*) Severity of reaction elicited by the primary stimulation.

The other factors are

(*d*) Age. (*e*) Sex. (*f*) individual constitution, (*g*) nature of illness and the (*h*) route of administration.

Thus in febrile conditions like Pneumonia the dose is to be less than optimum for fear of causing hyperpyrexia over and above the pyrexia present.

The dose is proportionately reduced in children and in severe infective conditions In all such cases of doubt it is advisable to start with an experimental dose, while subsequent local, general and focal reactions to this dose will guide the subsequent. (*i*) Last but not least, time factor plays an important role and so far no fixed arbitrary period of intervals as 3, 5 or 7 days has been chalked out, the nature of reaction being the guide. To avoid error prolonged intervals must be avoided and thereby one can easily overcome the much exaggerated danger of negative phase and shock.

III. *Physical State of patient* :—Leucocytic activity deteriorates with advancing age. This fact has been confirmed experimentally and certainly favours a young child in combating the infection better.

Drugs like Alcohol, Ether Chloroform and other narcotics reduce the body resistance to infection and this explains why Alcoholics fall an easy prey to it.

General body resistance is also manipulated by several minor factors like duration of illness, nutrition and resistance of patient,

idiosyncracy and inbereted traits of physical constitution.

IV. *Mode of parenteral administration* :—

(*a*) Intra-muscular route is best the usual sites being upper third of arm, Gluteal region and abdominal parieties, and these routes are chosen respectively with increasing amount of antigen to be given. The action occurs in a longer time than the intravenous route, but certainly the risks of undesirable effects and complications is less.

(*b*) *Intravenous route*':—Is the routine preferred in cases where sharper and quicker reaction is desired but is certainly risky. The disadvantages being greater have outweighed its advantages and so the technique has gone out of repute.

(*c*) *Intra-dermal route*—has been employed but its advantages are of doubtful value and hence is seldom used—reactions are milder and delayed.

V. *Number of previous injections* :—Production of shock due to miscalculated dosage and spacing of stimuli has long been apprehended but practically none of these cases show this hypothetical condition.

Conclusions :—After having considered the various factors modifying immunity reactions examples have been seen where sthee factors being constant. Variation has been observed. Explanation in these cases is "difference in immunity response of the body cells" a factor which is exceedingly variable and fluctuating. This great variation in effects, the dangor of eliciting too much reaction and lack of standardised products greatly complicates the non-specific protein therapy.

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UTERINE INVERSION*

A CRITICAL REVIEW OF THE TREATMENT

By MISS J. JHIRAD, M.D.

Inversion is fortunately a rare occurrence. Its frequency (puerperal) has been stated variously as 1 in 750,000 to 1 in 4,300 (Brett) (6) and as 1 in 10,000 to 1 in 200,000 (Peel) (31). Probhodh Das (32) from a review of literature gives an incidence of 1 in 14,881. Munro Kerr quotes Jardine giving a frequency of 1 in 17,000. It is impossible to gauge the frequency in India where proper notification of births and deaths and supervision of puerperal cases is not carried out.

For purposes of management, cases of inversion have been considered under the following headings :—

1. Puerperal—(*a*) Acute—within 48 hours. (*b*) Sub-acute from the third day to the end of one month, (*c*) Chronic after one month (Kellogg).
2. Pathological—due to tumours.
3. Idiopathic—referred to by many (less than 2 per cent).

The chief principles in the treatment of acute cases are promptness in controlling haemorrhage, combating shock and reduction. The latter treatment should however not be carried out in face of marked shock. Reduction under adequate anaesthesia is usually easy. I have no personal experience of such cases as I have never had occasion to treat them. The only case I have seen was one in my Residentship at Birmingham (1918) when a case seen by an Honorary at the patient's house was sent into hospital and promptly replaced by the Honorary under anaesthesia given by myself. This patient showed signs of recent haemorrhage but was not profoundly shocked. Her convalescence was uneventful.

Miles Philips (1) advises treatment of shock first and reduction latter. If cases are not reduced within 48 hours of occurrence the chances of contraction of the cervical ring are increased and consequently the possibility of reduction more remote. For these subacute cases, various measures have been suggested :—

1. Manual taxis under anaesthesia.
2. Aveling's Repositor.
3. Huntington's operation (abdominal reposition).

* Paper read at the meeting of the Bombay Obstetric and Gynecological Society on the 15th November 1945.

The probability of spontaneous reduction must, however, be borne in mind. McCullagh (2) in his lucid article, refers to this possibility and reports four collected from literature amongst 200 puerperal inversions. He mentions a case of his own in which spontaneous reduction occurred whilst awaiting a third application of Aveling's. Berkeley (3) has reported two cases, Blair Bell, (4) one and Barrows (5) reports one case in his series of five. We had one case in our hospital brought in 24 hours after labour at home, attended by a dai, a young primipara. The inverted uterus protruded beyond the introitus and presented a very sloughy surface. The patient ran a stormy course, but gradually as the infection cleared up, the uterus receded into the vagina. She was then put into Trendelenburg posture and douches given, following by glycerine instillations into the vagina in anticipation of manual replacement under anaesthesia. A vaginal examination had been made to see the condition of the uterus. Ten days later to our surprise, when examined under anaesthesia, the uterus was found to have reduced itself.

Manual taxis, if the direction of force is correct, will be found successful in a good percentage of cases but it is surprising how firm the cervical ring can get and how fibrous the uterine wall even at this early stage.

Aveling's Repositor has been credited with much success by British Gynaecologist, and should prove useful in these sub-acute cases. McCullagh States that the repositor is invariably successful after two weeks' treatment.

The American Gynaecologist do not seem to have been quite at impressed with the method and the majority advocate *Huntington's abdominal reduction* in which after opening the abdomen the uterus is gradually pulled up by Allis's forceps on either side replacing further on the body of the uterus as it is raised up.

Brett (6) advises watchful expectancy for six weeks, and suggests that the inversion may reduce itself. He advocates Huntington's operation, failing which he advises Haultain's operation. Huntington, Irving and Kellogg (7) report five cases treated by their method, three treated after failure with manual taxis, and two treated without attempts at taxis. All five recovered although pulseless when operated on.

For the chronic case, the same measures as for the sub-acute type may be tried with varying success. Taxis and repositor have proved successful in some hands and deserve to be considered prior to resorting to drastic measures. Swayne (8) in his article on chronic inversion in System of Gynaecology gives the following reasons for failure of manual taxis :—

1. Inability to dilate cervical ring.
2. Adhesions of peritoneal surface.

3. Rigidity of walls due to fibrous degeneration.

He mentions that laceration of the vagina or perforation of the uterine wall are distinct dangers of these manipulations, which are also followed by constitutional disturbances. According to McCullagh, manual reduction usually fails. It is important to realise that the force used for reduction should be guarded for fear of formidable injury to soft tissues. The repositor is a safer procedure as the force used is indirect. Aveling (9) was one of the greatest advocates of this method of reduction and his model is the most popular. He gave a demonstration of his method and reported 11 cases treated successfully. To achieve success the repositor *must be made specially to fit each case* and the direction of traction adjusted carefully.

Quoting Swayne again, the repositor method may be unsuccessful, 1. for want of dexterity of power, 2. peritoneal adhesions, 3. pressure of constriction ring, and 4. most important of all, rigid and fibrotic uterine wall.

Munro Kerr (10) avers that 90 per cent chronic inversions are replaceable by Aveling's repositor. McCullagh is also an advocate of the repositor. Miles Philips (11) reported a case of four months duration cured by the repositor within 12 hrs., and one of Favell's reduced in 48 hrs. Donald (12) reported success in four cases. Quigley (13) reports a case with repeated haemorrhage replaced by Aveling's repositor. Haig Fergussan (14) reporting 4 chronic cases treated surgically opines that taxis and repositor are suitable for recent cases. Spencer (1919) maintains that all inversions, however, chronic, can be reduced.

To go on to *surgical measures*, various operative procedures are available. Of these, *Spinelli* finds most favour in the vaginal methods, and Huntington's, Haultain's and Dobbin's for abdominal route. Hysterectomy is rarely to be considered in chronic puerperal cases as these are seen most commonly in young primiparous women.

Spinelli's has perhaps been one of the most popular operations. Swayne in his articles advocates it, and so does Davis (15). Various individual operators, West and Camben (16), Aranow (17), Barrows (18) Pelton Tew (19), Treston (20), Leroux (21) have reported good results with this operation. Crosser (22), gives a detailed description of this method and remarks that the uterine wall was so fibrotic, no repositor could have helped, the case in his opinion being a good illustration of the difficulties encountered with fibrotic changes.

Huntington's operation is perhaps more suitable for sub-acute cases as the constriction of the cervical ring would be difficult to overcome in the chronic cases. According to Davis, in only one-third of the cases treated by laporotomy could the cervical ring be dilated. Haultain's operation (1901) in which the ring is divided posteriorily after opening the abdomen, has found much favour in a wide circle. Wilson (23) is a strong advocate of the operation.

Gordon (24), Barrows (5), and Haig Fergusson (14), have reported cases treated by this operation. Dobbin's operation (1905) in which the anterior part of the cervical ring is incised after laporotomy, has been described and illustrated by various authors but hardly any cases are reported. McCullagh (2) and Brett (6) recommend this operation in their reviews. Wilson claims simplicity of technique and shorter incision over uterus, for Haultain's operation.

It is not ponsible to be too dogmatic over the choice of operation for a given case, for each case must present peculiaritics demanding special consideration. Certain advantages and disadvantages have been referred to by advocates of the various operations. Conservative operative procedures will be considered suitable only in the absence of septic infection.

The advocates of vaginal aperation (particularly Spinelli's) maintain that there is less shock rnd less sepsis with this procedure. Davis agrees with the above statemeut but suggests that the one advantage claimed for the abdominal route is that existing adhesions may be tackled. Gordon (25), during discussion of Aronow's case treated by Spinelli's advocated Huntington's abdominal operation and stated the advantages of the abdominal routes as follows:— 1. much better exposure. 2. much less bleeding. 3. less trauma to uterus. 4. woman left in much safer condition for future pregnancy. 5. hysterectomy done more readily if deemed necessary.

The test of these conservative operative procedures lies in their immediate mortality and morbidity rates, and finally on their influence on the course of further pregnancy and labour. The abdominal route is considered safer from this point of view, whereas rupture of the uterus has been reported after Spinelli's. Gordon (26) and Barrows (18) each report a case of rupture, while Miller (27) reports five cases (after Spinelli's) having had normal labours. West and Camden (16) report a case ending suecessfully.

According to Miller who collected 56 cases from the literature for a follow up of their pregnancy and labour, there was an incidence of 44 per cent recurrences after manual replacement (25 cases), whereas there were none in operated cases (22 cases), five of which were Spinelli's.

The incidence of chronic puerperal inversion has been variously stated as 43 per cent (Crossen) of total acute inversions, (Crampton), 17 per cent and 26 per cent (Thorn).

Thorn in a review of 128 cases gives a mortality of 21 per cent in cases replaced by laporotomy, as against 6 per cent after vaginal hysterectomy. In McCullagh's collected series of 200 puerperal inversions the mortality rate was about 17 per cent for both vaginal and abdominal operations.

I can claim very limited experience of cases of chronic inversion. Since 1925, I had occasion to treat in collaboration with my colleagues

at the Cama Hospital two cases of sub-acute inversion, eight of chronic puerperal inversion and two of path logical ones. The last two I shall refer to later. The histories of the puerperal cases are as follows:—

1. Multipara. aged 30, continuous bleeding one year. Since a miscarriage at 5 mths—very anaemic and wasted chronic inversion—cervical ring hardly felt. Attempts at reduction failed but vaginal wall lacerated one side and had to be sutured. Repositor got made and tried 3 mths later—unsuccessful—(it was felt that the repositor had not been made to fit properly) Spinelli's operation—drainage anterior and posterior pouch—kept up temperature four days and had offensive discharge. The uterus was freely mobile and no pelvic masses were felt when examined prior to discharge.

2. Multipara, aged 30, continuous bleeding for one year since confinement which was attended by a dai. According to patient's version, placenta was either pulled or pushed—anaemic—cervical ring felt all round inverted uterus—reduction attempted but failed. Spinelli's one week later—uterus very fibruous—anterior drain—high temperature with rigors for two days. Uterus freely mobile on discharge.

3. Primipara, aged 20 N. D. 2 years ago child died later—attended by a dai—had D. P. H.—ill for 1½ mths. Profuse and prolonged periods since 10-12/28 whitest—no pain or backache. Very anaemic—cervical ring slack but fibrous. Reduction attempted failing which Spinelli done at the same sitting—uterine wall thick and fibrous, sutured under strain even after excision of wedges.—Anterior and posterior drains—high temperature first week—signs of pelvic peritonitis—developed a left sided pelvic mass which subsided slowly.

4. Primipara, aged 20, N. D. two years ago but difficulty with placenta, irregular bleeding since partus—dull lower abdominal pain and backache—whitest—very anaemic—small inverted uterus—Spinelli's anterior—drain—temperature for 24 hrs.—later satisfactory.

5. Primipara, aged 30, delivery 10 years ago—placenta removed by dai—was unconscious—continuous bleeding since partus. Very anaemic repositor tried 48 hrs. (not specially made to fit) Spinelli's—anterior drain—temperature 24 hours—later satisfactory.

6. Primipara, aged 18, delivery four years ago. P. P. H. placenta removed by dai—continuous bleeding since partus—very pale. Spinelli's (attempted peripheral taxis incising ring)—wall very fibrous—anterior and posterior drain—slight general disturbance—highest 104 F, only one—was given prophylactic sulphonamide therapy—mild local sepsis—uterus mobile with no lateral masses, on discharge.

7. Primipara, aged 20—irregular bleeding one month since a probable abortion of 3 mths.—one F.T.N.D. 7 years ago. Anaemic—

cervical lips flush with vaginal vault—put in Tredelenberg posture and given glycerine instillations into vagina for two weeks after which Haulain's operation (Huntington's method tried but failed). Incision posteriorily into cervical ring and uterus pushed up by pressure through pelvic tissues—during reduction, spontaneous extension of incision up towards fundus was noticed to occur—sutured in two layers slight tension but no need for paring of edges felt—posterior drain progress uneventful—no temperature.

8. Second para—aged 19.—N. Ls —D. P. H. and shock (attended by dai) seen soon after delivered by a consultant who treated her for shock, and advised removal to hospital which was not done continuous bleeding for two months, followed by two months amenorrhees—Aveling's Repositor tried (not specially prepared) two months prior to operation unsuccessful—operated four months after delivery. Laparotomy and anterior incision into cervical ring after reflecting peritoneum of anterior pouch. Dobbin's method. Uterus pushed up by pressure through pelvic tissues—again incision noticed to extend spontaneously up body of uterus during reduction.—suture of uterine wall under slight tension. No drainage—progress satisfactory—on temperature. (By courtesy of Mrs. Wadia—a case at her Nursing Home.)

9. Sub-acute case, Multipara, aged 26.—Spontaneous inversion of uterus soon after N. D. after a strong pain—attended by a midwife—placenta separated snd uterus pushed up by midwife—had P.P.H. Inversion noticed again on the seventh day—seen at hospital at the end of a month—manual taxis failed—Aveling's repositor tried, but probably not fitted properly. Two months later Spinelli's with sterilization (at patient's request) Reduction attempted after cutting ring but failed Anterior and posterior drain—localised paritonitis leading to slight infiltration which cleared up.

10. Case of spontaneous reduction already related on page.

Commentary.—One feels that some of the cases seen fairly early should have yielded to conservative measures. It is conceded that in more skilled hands this would have been achieved. I must admit the repositor being ill-fitted in most cases, was not given proper trial to.

A series of cases in the beginning were treated by the Spinelli's operation, as it was felt that the uterus chronically inverted, being potentially septic, abdominal methods would be detrimental. Spinolli's was found quite fascinating although it meant working in a cramped up space. For none of the cases was the paravaginal incision deemed necessary.

The most striking fact was the rigid fibrous uterine wall, even in the fairly recent cases. Each case needed full incisions right up to and almost over the fundus, to bring about reduction, and wedge-shaped excisions, ere apposition could be achieved. This rigidity

was noticed even in those cases treated by abdominal section, as note the spontaneous extension of incision half way up the fundus during reduction. It may be argued that the force used to push up the uterus was inadvertently too strenuous. Certainly very great care has to be taken to guard against violent taxis.

After noticing the way the uterine wall gave way in both the cases treated by laparotomy, one feels that one cannot be too careful in one's attempts at vaginal taxis, as even if reduction is achieved, the possibility of rupture of the uterus is great.

A review of the cases treated makes one feel that the *constricting ring of the cervix* was not as great an impediment to reduction as the *rigid, fibrous and inelastic uterine wall.* Swayne and Crossen have both emphasised this rigidity and the consequent difficulty.

Although Haultain's method has been advocated by many it seemed to me after my first attempt at this operation that a scar on the posterior wall of the uterus would not be too ideal, as adhesions would be liable to form with greater ease I started devising an anterior operation in my mind and fortunately saw a case where we could put it into operation. Later on, on re-reading the literature I came across Dobbin's operation.

The advantage of this over Haultain's seems to me to lie in the fact that the anterior peritoneum can be reflected to separate the bladder wall and the flap of peritoneum used later to cover most of the suture line.

An analogy may be drawn to the lower segment Cæsarean. If the incision does have to go up along the body, being on the anterior wall it is turned away from the rest of the peritoneal cavity and thus the liability to adhesion is minimised. Again one is reminded of the preference to interior wall in the classical Cæsareun, and Bonney's method of myomectomy.

I feel a more extensive trial needs to be given to Dobbin's method.

We have two abdominal versus seven Spinelli's to our credit and I must say the abdominal method seems simpler as the space is not cramped, and the general disturbance is less on the whole. I have not noticed shock in these two cases. It is obvious that the vaginal manipulations of the inverted uterus add to the risk of infection. Our two abdominals, in which we aided reduction by pressure through the pelvic tissues and not by an assistant working through the vagina, had no constitutional disturbance and no signs of infection, whereas most of the cases treated by Spinelli's when the inverted fundus had to be handled, showed variable amount of constitutional disturbance, while those in which partial attempts at reduction, before or after incising the cervical ring were made, developed distinct signs of pelvic peritonitis.

It is realised that operative procedures should not be combined with attempts at taxis.

The first case (Haultain's) we did under spinal and I felt that might have prevented proper relaxation of the cervical ring and yet Hunter reported marked relaxation of the cervix under spinal in cases of difficult labour. The next was cases operated on under ether anæsthesia with no better relaxation of the ring. It is possible that gas and oxygen may give better relaxation. The case with which even elderly nulliparous cervices can be dilated under gas encourages one to anticipate similar aid in these cases.

Pathological Inversions.

The incidence of these is very low. McCullagh (2) in his review of 233 cases found 33 only as against 200 puerperal inversions. Thorn in 1911 collected 457 cases of which 83 were due to neoplasms, an incidence of 19 per cent.

The commonest cause is said to be fibro-myoma : of the malignant group, sarcoma is the commoner type, carcinoma being considered very rare. In the 83 cases of neoplasms collected by Thorn, only 5 were malignant four being definitely sarcomata and the fifth doubtful.

McCullagh found 6 cases of malignancy in the series collected by him but three of these had carcinoma. Williamson and Abercombie (28) report a case (included in McCullagh's series) of inversion by squamous celled carcinoma of the fundus in a woman of 54, two years after menopause. She gave a history of bloodstained discharge with attacks of bleeding of seven months' duration, followed two months later by stress incontinuence. A sloughing mass with inverted uterus was found. The uterus was partially removed and treatment by Radium instituted, followed two weeks later by panhysterectomy. They feel that the squamous-celled carcinoma was probably responsible for the inversion.

Haig Fergusson (14) reported four cases, two puerperal, and two pathological, the latter being due to fibroid polyp and adeno-carcinoma respectively. Both the cases were treated by vaginal hysterectomy. Blair Bell (4) reported one acute and one chronic inversion, the latter in a woman of 58, with history of menopause of 7 years. The inversion was due to fibro-myoma undergoing necrotic changes. He excised the necrotic tumour and later performed hysterectomy. He stresses central insertion of the placenta or tumour as a leading etiological factor. Kedarnath Das (29) reported eight cases, four of which were pathological, all being due to sloughing fibroids. He advised hysterectomy for such cases. Fairlie (30) reports two cases both due to fibromymata. He removed the tumour in each case and replaced the uterus.

We came across a case in 1939 of a woman aged 28, who gave a history of a prolapse starting from the second day of her delivery

8 years ago. Her first was a full-term ehlld, liviug and the socond one premoture two years later. Periods which were regular prior to her first delivery had been coming on at intervals of 3-4 months and lasting 8-10 days. The last period had come on after 2½ months and was just over before admission. There was a history of whites for only three months. She was a pale, flabby woman. On local examination, a slough friable growth filled the vagina and a narrow smooth pedicle attached to the cervixbimanual was difficult. After ten days' treatment, she was anæthesised and a well defined cauliflower growth with inversion was diagnosed. The uterus was amputated at the junction of the cervix and the peritoneal cavity drained. The patient died of peritonitis on the fifth day. Report on the tumour was squamouscelled carcinoma. The patient's history was very vague, but the fact that her periods came on at long intervals negatived the possibility of chronic inversion of some years standing. It is more probable that the carcinoma was responsible for the inversion.

Another case of pathological inversion at our institution was in a case associated with a fibroid also seen in 1939. She was a woman of 40, with a history of bleeding for ten months and pain in abdomen of same duration. She had had five children, the last being ten years ago, after which she had no period for over nine years. She was also a pale flabby woman. Local examination revealed a polypoid mass in vagina the cervical rim could not be felt. She bled freely particularly alter examination, and required blood transfusion. Two months later she was operated on and a vaginal hysterectomy was performed. There was a fibroid the size of a large lemon, eccentrically situated at fundus. She evinced signs of pelvic peritonitis but made a good recovery.

It is apparent that the fibroid was responsible for the inversion in this case, but the notable feature of the case is the fact that the fibroid had started growing nine years after a premature menopause, indicating the dormant powers of recoupment of the ovaries. In this case if the woman was younger, an enucication of the fibroid with replacemeht of the uterus might have been possible. But the history of prolonged amenorrhœa followed by symptoms and a tumour inversion kept the possibility of sarcomatous changes prominently in one's mind.

This dissertation on the incidence of chronic inversion and a review of the suggested treatment with notes of twelve cases seen personally, is presented with a view to get the ideas on this subject clarified and to invite further reports and suggestions from the more experienced gynæcologists.

DISCUSSION

A clinical meeting of the Bombay Obstetric and Gynæcological Society was held on Thursday the 15fh November 1945 at 7-30 p.m

at the Society's rooms, when Dr. Jhirad read a very instructive paper on "Inversion of the Uterus",

She reported 12 cases in her experience since the year 1925, 2 cases of subacute inversion, 3 of chronic puerperal inversion, and two of pathological ones. She commented that conservative measures should first be tried in cases seen early and that the repositor must be well-fitting in every individual cases. Of the operative procedures, she had very good results with Spinellis but she advocated a more extensive trial of Dobbin's operation. Both cases of pathological inversions were treated by viginal hysterectomy.

Dr. Sariya then reported a case of inversion of the uterus during a lower segment cæsarean section. After the delivery of a 9 lb. fœtus, the uterus was soft and flabby, the placenta still adherent, and a slight pull on the cord resulted in inversion of the fundus. There was serious bleeding. But the placenta was removed, the uterus corrected, and the bleeding controlled; patient doing well.

Dr. Kailas Singh of Indore, King Edward Medical School, reported a case of chronic puerperal inversion of the uterus treated by Haultain's method, she did well and menstruated quite normally but had not conceived since.

Dr. Ajinkya mentioned a case of chronic inversion with a pedunculated fibroid. Here on removing the fibroid the inversion corrected itself.

Dr. Karande reported two cases, one of a chronic inversion with a sub-mucous fibroid and another in which the uterine openings of the tubes could actually be seen.

Dr. B. N. Purandare reported two cases of acute puerperal inversion of the uterus; one which occurred immediately after the child was born with the placenta still attached to the fundus and the other which occurred immediately after the 3rd stage of labour. The latter patient, even after the replacement collapsed and died. He quoted another case of a big fibroid, which had mistaken for a twin foetus during labour by a practitioner. This patient whilst still in the puerperal ward, suddenly got inversion of the uterus, after catheterization. He also mentioned another case where the fundus of a chronic inversion, was so septic and foul smelling that it was diagnosed as cervical carcinoma. He demonstrated the specimen of the same uterus which was removed by vaginal hysterectomy.

Dr. J. M. De Sa Souza reported an unusual case of a chronic inversion of the uterus in a *nulipara* aged 18. She remarked that as the patient had never conceived, and there was therefore no obstetric cause to account for the inversion, neither was the inversion due to fibroid, polypus etc. The condition was diagnosed as a sub-mucous fibroid polypus. It was only when the surface of the supposed fibroid was incised, that the appearance of peritoneal

surface of the uterus, led to the diagnosis of chronic inversion. This step was undertaken only because the oozing was rather much for a submucous fibroid, which led Dr. H. De Sa to be rather suspicious. A sub-total hysterectomy was done, because of the atrophic condition of the tissues the stitches cut through and the edges of the uterine incision after a Spinelli's operation, which had been first tried, could not be brought together.

REPLY.

Dr. Jhirad in replying to the previous speakers remarked that in chronic inversion of the uterus the cervical ring is often better felt on making a rectal examination. She explained that in Dakins operation, it was first necessary to separate the bladder, before cutting the cervical ring.

Dr. Wadia stressed the importance of the fact that quite often a puerperal inversion is spontaneous and then thanked Dr. Jhirad for her very instructive paper.

Medical News & Notes.

PRESIDENT'S ADDRESS
AT THE
TWENTY FOURTH SESSION
OF THE
MEDICAL COUNCIL OF INDIA.

Members of the Council,

I welcome you to-day to the twenty-fourth Session of this Council. This is the first occasion on which it is my privilege to address you, and in doing so, I am highly sensible of the honour you have done me by electing me the President of the Council and of the high standard of this office which has been created by my predecessors. I appreciate the nice things that have been said about me by our Vice-President Dr. Vyas, who has been my colleague in the Council and the Executive Committee from the beginning.

2. I gave careful thought to the question as to whether these addresses were necessary. I am convinced that the Presidential Address, the practice of which was started in the year 1936 by our first President Sir Cuthbert Sprawson, afforded to the members of this Council and the public a concise survey of the activities of the Council. They also afford an opportunity for the President to make public announcements on important matters affecting the medical profession. I am, therefore, of the opinion that the practice established by my predecessors in this office should be continued.

3. You must have learnt with regret the retirement of General Hance, now Sir James Hance, and in consequence; of his resignation from this Council. You will, I am sure, join me in a cordial expression of the appreciation of his services to the Medical Council

of India and of our good wishes for his health and well being in h retirement.

4. I welcome General Hay, the new Director-General, India Medical Service, to the Council in the vacancy, caused by the resi nation of Sir James Hance; as also Dr. Sen Gupta, representing th medical graduates of Central Provinces and Berar, and Colon L. K. Ledger, representing the Government of Central Province and Berar.

5. As reported to you at the last session, the inspection of th Hyderabad Medical College affiliated to the Osmania University wa carried out on behalf of this Council by Colonel Jalal Shah an Dr. S. N. Mathur in April last year and their reports were forwarde to the Hyderabad State Medical Council for observations. These ar still awaited.

6. Your Executive Committee have considered the Inspectors' reports on the Professional Examinations for the M.B., B.S. degree of the Agra University together with the observations of the University thereon. Their recommendation is being submitted to you to-day.

7. With regard to the establishment of an All-India Medical Register, replies from all the Provincial Medical Councils have been received in connection with the note prepared by Dr. Bidhan Chandra Roy. This matter has received further consideration of your Executive Committee and their recommendation on the subject is being submitted to you to-day.

8. The Administrative Medical Heads of the Province have been addressed to furnish us with a list of the existing medical schools in their respective provinces still imparting instruction for the Licentiate standard. They have also been requested to intimate as to which schools are being raised to the University standard.

9. The latest recommendations of your Council regarding concessions to be granted to the Licentiates to enable them to take M.B., B.S. degrees of the Universities have been forwarded to all the British Indian Universities on our First Schedule. I appeal to the representatives of the Universities to use their influence to obtain these concessions for the Licentiates.

10. It is useful to review at intervals our achievements and our failures so that in the light of experience we may better plan our future.

11. This Council was created under the Indian Medical Council Act of 1933 and first met in 1934. The record of our achievements at home since then is certainly creditable. We have been able to "establish a uniform minimum standard of higher qualifications in medicine for all provinces." To achieve this we laid down minimum standard of professional education and of professional examination; carried out a series of inspections of the Universities in

British India, advised them whenever necessary, laid down the qualifications required for teachers and examiners — and framed the courses of study for Inter. Science Students in the Basic Sciences of Chemistry, Physics and Biology suitable for Medical Students. The extensive literature produced by our inspectors, visitors and experts is itself a valuable mine of information on medical education in India, and is worth publishing in a separate volume, as nowhere else is such information available.

12. We have been largely responsible for the abolition of the licentiate teaching in many of our provinces and the conversion of some of the medical schools of the licentiate standard to the colleges affiliated to the Universities. One of the non-University qualifications is already on our First Schedule as a result of our inspection — namely M.C.P.S. of Bombay. We are trying with some success — to persuade the Universities to give special concessions to the Licentiates to enable them to take the M.B., B.S. degrees of the Universities. We have gone beyond the limits of British India into the Indian States of Hyderabad and Mysore, inspecting their Universities, giving all the advice we could give to raise their standards sufficiently enough to come in line with the Universities in British India and thus establish reciprocity.

13. What about our efforts to secure honour abroad?

It is true that this Council was soon able to establish relations with General Medical Council which may be called truly reciprocal as far as most of the Universities on Schedule I are concerned. But the General Medical Council recognises the degrees of the Patna University when granted on or before 11th May 1935 and those of Calcutta University when granted on or before 16th October, 1936. Andhra University degrees are not recognised at all. Thus anyone on the British Register may practise in any part of British India including Andhra Desh but no graduate of the Andhra University, and not all the graduates of the Calcutta and Patna Universities can practise in Great Britain. Indeed though we have found two British qualifications not upto our standard, we have been so far unable to remove these from our Schedule II. This position cannot be said to be fair — nor can we call it perfect reciprocity. I trust we will be able to settle those differences with the General Medical Council in the near future. I assure the General Medical Council that there is plenty of good-will on our side.

14. When we turn to other countries, we cannot but feel humuliation and resentment at the attitude of these countries. Even in India itself our graduates cannot practise in French India whilst practitioners with French India qualifications can do so in British India and this, in spite of correspondence since 1936 and in spite of the appeals of your Executive Committee and the resolutions of the Madras Medical Council endorsed by other Provincial

Councils, to enact suitable legislation to 'Prevent practitioners from French India from practising in British India.'

15. In 1936, we opened negotiations with a whole lot of countries to establish reciprocity with them. Only four were willing to have reciprocity directly with us, fourteen insisted on indirect reciprocity through General Medical Council of Great Britain, whilst the rest did not choose even to reply. We then agreed to indirect reciprocity in 1937. Experience soon taught us that this was neither workable nor consistent with our honour. At our recommendation therefore in 1940 the Government of India abolished indirect reciprocity. To-day, we have direct reciprocity with three countries only — Burma, Malta and New Zealand — Burma rather grudgingly and very ungraciously.

16. This Council has tried its best to secure honour abroad. It has failed because the politicians who created this Council did not arm it with sufficient powers. The same politicians will have to see to it that our honour abroad is not at a discount. I for one have often wondered what is the sense of reciprocity — direct or indirect — with countries that will not allow Indian Nationals to settle there even though, they may recognise our Indian degrees. The negotiations that are going on just now with South Africa seem to me futile and undignified. It is for you to decide your attitude on such questions in the future; but I cannot speak out what is on my mind and most likely on yours.

17. What of the future? We will have to see that the efficiency attained at home is maintained and further strengthened in the light of our and world experience. We have before us now the Bhore Committee Report, and fortunately we have amongst us some who were members of that Committee and helped to shape that report. We will study it carefully. A statement has been drawn up by our Secretary in connection with the recommendations of the Bhore Committee Report as far as they concern the Medical Council of India. This statement will be printed and supplied not only to the Members of this Council but also the heads of various medical institutions and Universities so that it may help them to study the four volumes of the Bhore Committee Report. After this, in case a reference is made to us by the Central Government as to our opinion on the Bhore Committee Report, we hope to have a special meeting of the Executive Committee somewhere at the end of July and, if necessary, if the matter is very urgent, we may have to call a special meeting of this Council to consider the recommendations of the Bhore Committee as far as they concern this Council. We hope, therefore, that the statement that will be sent out to you, will be helpful in studying the recommendations of the Bhore Committee.

18. It is now 12 years since we inspected the Universities and a fresh inspection is overdue, more particularly as new Medical Colleges are being added.

19. We will continue our efforts to have an all India Medical Register. We must bring about adjustments of the functions of the Provincial Councils with ours. We must approach the Central Government to give us proper safeguards and sufficient powers, so that reciprocity shall be fair.

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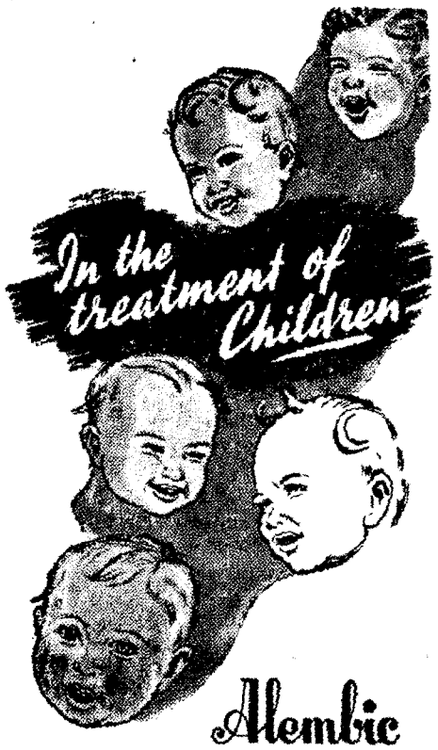

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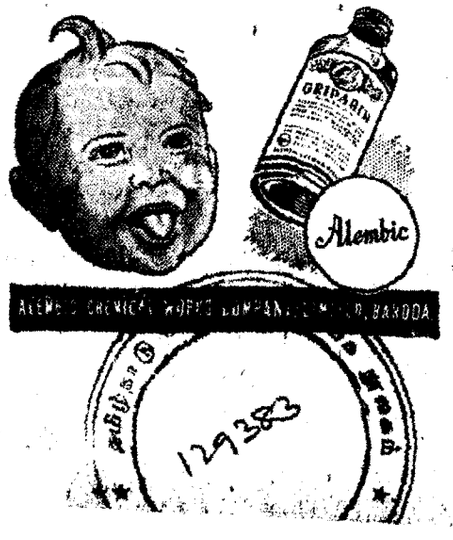

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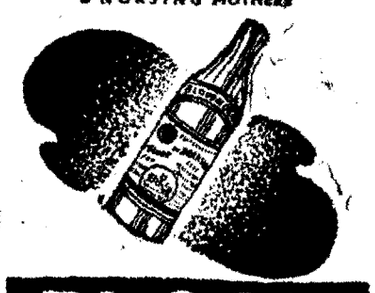

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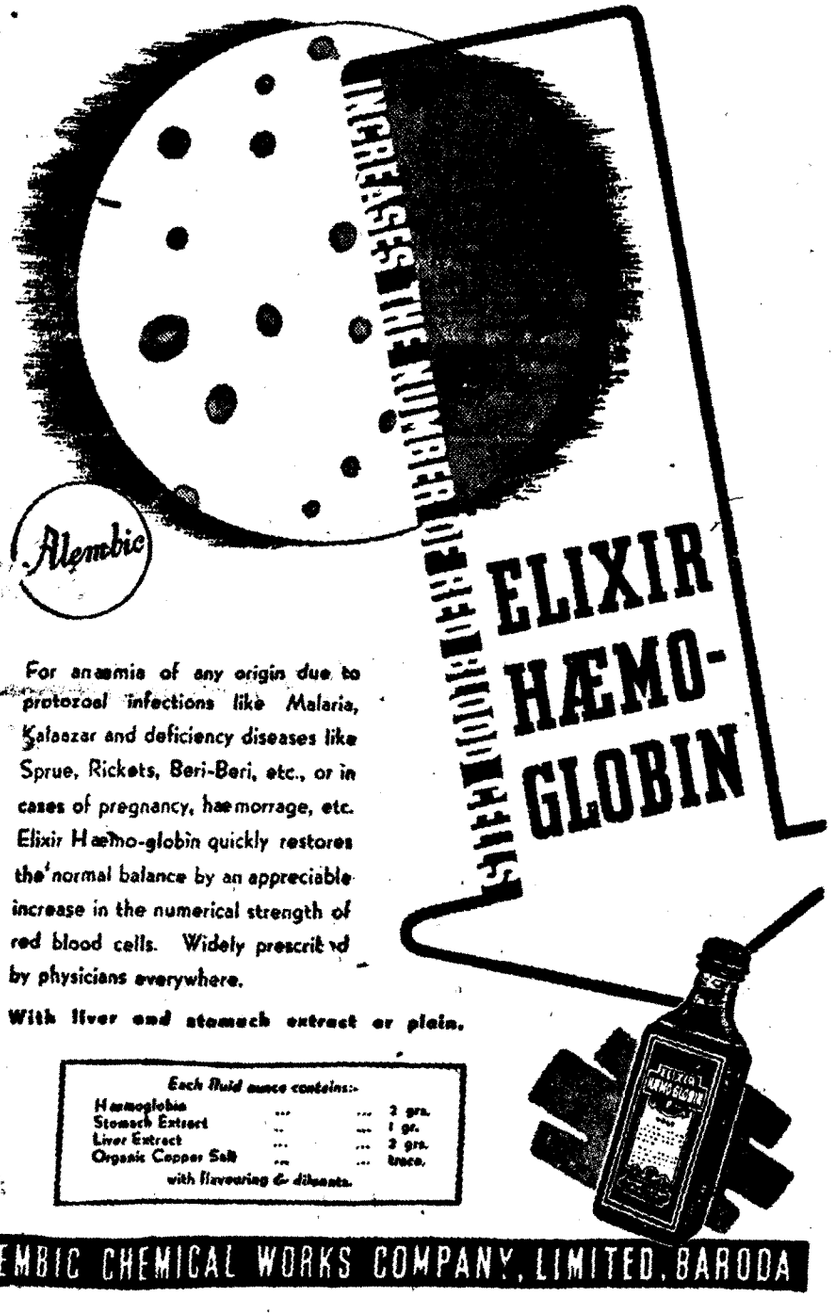

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