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FOREWORD

This year is the centenary of the discovery of malaria transmission by mosquitoes made by Sir Ronald Ross in August 1897. Sir Ronald Ross (1857-1932) was born on 13th May, 1857 in Almora, a hill station in Uttar Pradesh, India. He received his medical education at St. Bartholomew's Hospital, Great Britain. In 1891, he entered the Indian Medical Service. He had many interests and talents. He studied world's poets and the classics, wrote poems, dramas and novels, learnt Italian, French and German and was deeply interested in mathematics. He married Rosa Bessie in 1889.

Sir Ronald Ross met Dr. Patrick Manson on his second visit to England in 1894. This association of two great men is one of the most fascinating romance in the history of tropical medicine. After several years of painstaking work on the mosquito-malaria hypothesis, on 20th August, 1897 Ronald Ross found oocysts on the stomach wall of dappled winged mosquitoes (probably *Anopheles stephensi*). This epoch making discovery was made while working in a small laboratory in Secunderabad, India. He then wrote the following sonnetelles to his wife :

This day relenting God
Hath placed within my hand
A wondrous thing; and God
Be praised. At His command,

Seeking His secret deeds
With tears and toiling breath
I find thy cunning seeds,
O Million-murdering Death.

I know this little thing
A myriad men will save.
O Death, where is thy sting,
Thy victory, O Grave !

About this discovery Ross writes : "On turning to the stomach with an oil-immersion lens I was struck at once by the appearance of some cells which seemed to be slightly more substantial than the cells of the mosquito's stomach usually are, still very delicate and colourless. There were a dozen of them lying among cells of the upper half of the organ and though, somewhat more solid than these, contained granules of black pigment similar to that of Plasmodium in finger blood ! They varied from 12 to 16 μm in diameter and were full of stationary vacuoles".

Good scientist that he was, he felt that any report of something new would meet criticism. Therefore to be prepared to answer the objections and somehow make them see too, he fixed and sealed the peculiar cells to be sent to Dr. Patrick Manson.

Next day on 21st August, the last remaining mosquito was also dissected. It contained similar cells but were somewhat larger, more distinct and with a thicker, perhaps double outline than those seen the previous day. The preparations of the stomachs were afterwards examined by Dr. Patrick Manson, Thin and Mr. Bland Sutton. The account of this important work of Ross and the observations of these scientists were published in 18th December 1897 issue of the *British Medical Journal.* Dr. Manson was inclined to believe that "Ross might have found the extracorporeal phase of malaria," but reserved his affirmation until more observations with stained specimens. Mr. Bland Sutton thoroughly endorsed Dr. Manson's opinion. Whereas Dr. Thin disagreed and said that the objects referred to were epithelial cells of the stomach that had undergone some unspecified change. But Ross had reason enough to think he was "on it". He was sure that the pigmented cells were in fact an incarnation of *Plasmodium* in the mosquito. As such, it justified Ross' excitement and even his decision to mark the 20th of August 1897 as the "Mosquito Day".

On the 100th year of discovery of mosquito phase of malaria, the Indian Society for Parasitology is organising "II Global Meet on Parasitic Diseases with a Focus on Malaria" from 18-22 August, 1997 in Hyderabad. Dates of the conference have been fixed to coincide with the Discovery Day. On this day commemorative stamp and first day cover would also be released. Ross's laboratory is being renovated and a function would be held to unveil the bust of Sir Ronald Ross at Begumpet, Secunderabad. World's leading malariologists will assemble in Secunderabad on this occasion.

This issue is dedicated to Sir Ronald Ross and contains articles on some aspects of his biography and contemporary research at the turn of the 19th century. Ross' original paper of his historic discovery is being reproduced as the leading article. Also included is the bibliography of the published works of Sir Ronald Ross.

(V.P. SHARMA)

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Note: The editor assumes no responsibility for the statements and opinions expressed by the contributors.

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On Some Peculiar Pigmented Cells Found in Two Mosquitoes Fed on Malarial Blood.

By Surgeon-Major RONALD ROSS, I.M.S.,
(With Note by Surgeon-Major SMYTH, M.D., I.M.S.)

For the last two years I have been endeavouring to cultivate the parasite of malaria in the mosquito. The method adopted has been to feed mosquitoes, bred in bottles from the larva, on patients having crescents in the blood, and then to examine their tissues for parasites similar to the haemamoeba in man. The study is a difficult one, as there is no *a priori* indication of what the derived parasite will be like precisely, nor in what particular species of insect the experiment will be successful, while the investigation requires a thorough knowledge of the minute anatomy of the mosquito. Hitherto the species employed have been mostly brindled and grey varieties of the insect; but though I have been able to find no fewer than six new parasites of the mosquito, namely a nematode, a fungus, a gregarine, a sarcosporidium (?), a coccidium (?), and certain swarm spores in the stomach, besides one or two doubtfully parasitic forms, I have not yet succeeded in tracing any parasite to the ingestion of malarial blood, nor in observing special protozoa in the evacuations due to such ingestion. Lately, however, on abandoning the brindled and grey mosquitoes and commencing similar work on a new, brown species, of which I have as yet obtained very few individuals, I succeeded in finding in two of them certain remarkable and suspicious cells containing pigment identical in appearance to that of the parasite of malaria. As these cells appear to me to be very worthy of attention, while the peculiar species of mosquito seems most unfortunately to be so rare in this place that it may be a long time before I can procure any more for further study, I think

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it would be advisable to place on record a brief description both of the cells and of the mosquitoes.

The latter are a large brown species, biting well in the day time, and incidentally found to be capable of harbouring the filaria sanguinis hominis. The back of the thorax and abdomen is a light fawn colour; the lower surface of the same, and the terminal segment of the body a dark chocolate brown. The wings are light brown to white, and have four dark spots on the anterior nervure. The haustellum and tarsi are brindled dark and light brown. The eggs– at least, when not fully developed– are shaped curiously like ancient boats with raised stern and prow, and have lines radiating from the concave border like banks of oars– so far as I have seen, a unique shape for mosquito's eggs. The species appears to belong to a family distinct from the ordinary brindled and grey insects; but there is an allied species here, only more slender, whiter, and much less voracious. My observations on the characteristics of these mosquitoes were not very careful, as when I first obtained them I did not anticipate any difficulty in procuring more.

On August 16th eight of them were fed on a patient whose blood contained fair to few crescents (and also filariae). Unfortunately four were killed at once for the study of flagellate bodies (flagellulae cysts). Of the remainder two were examined on the 18th and 20th respectively, without anything being noted. The seventh insect was also killed on the 20th, four days after having been fed. On turning to the stomach with an oil-immersion lens I was struck at once by the appearance of some cells which seemed to be slightly more substantial than the cells of the mosquitoe's stomach usually are. There were a dozen of them lying among (or within?) the cells of the upper half of the organ, and, though somewhat more solid than these, still very delicate and colourless. They were round or oval, 12 μ to 16 μ in diameter when not compressed (that is, considerably larger than the largest haemamoeba in man); the outline sharp but very fine; the contents full of stationary vacuoles; and no sign of apparent nucleus, contractile vesicle or amoeboid or intracellular movement. So far it would have been impossible for any but a person very familiar with the insect's anatomy to have distinguished them from the neighbouring cells; but what now arrested attention was the fact that each of these bodies contained a few granules of black pigment absolutely identical in appearance with the well-known and characteristic pigment of the parasite of malaria (large quartans and crescent-derived spheres).

The granules were more scanty in comparison to the size of the cell than in the haemamoeba, and numbered from 10 to 20 in each. They were not dispersed throughout the cells, but were collected in groups, or arranged in lines transversely or peripherally, or in a small circle round the centre (just as in some forms of the haemamoeba). They were black or dark brown, and not refractive on change of focus. In some cases they showed rapid oscillation within a small range, but did not change their position. Owing to their blackness, so different from the bluish, yellow, and green granules and *debris* found in and about the neighbouring cells, they arrested the eye at once; and it must clearly be understood that I have not confounded them with normal objects. In short (except perhaps that rods were shorter or absent) these granules of pigment were indistinguishable from those of the haemamoeba.

The eighth and last mosquito was killed next day, five days after having been fed. The stomach contained precisely the same cells, 21 in all, again toward the oesophageal end of the organ. In this case, however, they were distinctly larger and more substantial than in the seventh mosquito, and had a decidedly thicker outline. The size (along the major axis) appeared now sometimes to reach nearly 20 μ on a rough computation made without a micrometer. There thus appeared to be a marked increase in bulk and definition between these cells of the fourth and fifth days, suggesting that they had grown in the interval.

Both specimens were irrigated with 40 per cent, formalin, and sealed. The result of the formalin was, as anticipated that the bodies became slightly more visible than before, as compared with the stomach cells.

In spite of all attempts, I have not yet succeeded in obtaining any more of the species of mosquito referred to. Thinking, however, that I may have overlooked these delicate cells in former dissections, I have again examined a large number of brindled and grey mosquitoes, fed on malarial blood. Their stomachs certainly contained no such cells. Next I caught by hand a number of the more slender and white, but allied, species already referred to (I have failed in finding their grubs also), and examined them. Some had not been fed at all, and others had fed themselves on (presumably) healthy blood, two, three, or four days previously. The results were again negative. I may add that I have not yet succeeded in getting this species fed on malarial blood.

To sum up: The cells appear to be very exceptional; they have as yet been found only in a single species of mosquito fed on malarial blood; they seem to grow between the fourth and fifth day; and they contain the characteristic pigment of the parasite of malaria. It would, of course, be absurd to attempt final conclusions as yet; but I think we may venture to draw some cautious inferences on these observations. First, as to the nature of the cells. Judging from the facts that the elementary cells of allied species of mosquitoes are always alike, or very similar, and that I have never observed such bodies in previous or subsequent dissections of mosquitoes (I suppose I must have examined quite a thousand more or less carefully by this time), we may reasonably conjecture that these are no normal physiological cells– in other words, that they are parasites; and this view is fortified by the comparative substantiality of the bodies, by the appearance of growth between the fourth and fifth days, and, most notably, by their possession of pigment, a substance in my experience certainly quite foreign to the physiological cells of the mosquito. Secondly, as to the connection of these presumable parasites with the parasite of malaria; they have been found in two consecutive insects fed on malarial blood (owing to their delicacy, and to my attention not having yet been attracted by them. I may have overlooked them in the fifth and sixth mosquitoes), a fact which may encourage us to believe that they may exist in a large percentage of similar insects similarly fed; and as they have not been found in an allied species fed on presumably healthy blood, we may hazard a conjecture that their presence in the original species was due to the ingestion of malarial blood. These considerations, taken together with the remarkable fact that the cells contain pigment just like that of the haemamoeba (a characteristic product which is, I believe, unknown in any other protozoa except some allied haematozoa) seem to open the question of their being indeed the form of the haemamoeba we are in search of– namely, the alternative form in the mosquito of the parasite of malaria in man.

On the other hand, the parasitic nature of the cells cannot finally be accepted until certain facts as to structure, sporulation, and so on, have been demonstrated. Even if this be done, it remains to be seen whether the bodies are not parasites common in the particular species of mosquito referred to, and quite independent of the ingestion of malarial blood and of the haemamoeba in man. I must, however, confess to feeling personally that the presence of pigment is indistinctive of the haemamoeba, renders this last supposition rather unlikely.

In conclusion, I may note that the pigment in the cells may be derived from the haemoglobin in the insects stomach, in the walls of which the cells are situated. With reference to their being found as yet only in one species of mosquito, it may be remembered that Manson originally conjectured that each species of haemamoeba might require a special species of mosquito for development extraneous to man, just as filaria embryos do.

The two specimens containing the cells described above will be forwarded to Dr. Manson. Former specimens of microscopic objects sent to England by me have perished *en route*, and lest these should experience a similar fate I have thought it well to have an independent note on the subject on record. With this object I append a description of the cells furnished by Surgeon-Major Smyth who was very kindly examined the specimens. I should add that his measurements, made with a micrometer, are more exact than mine.

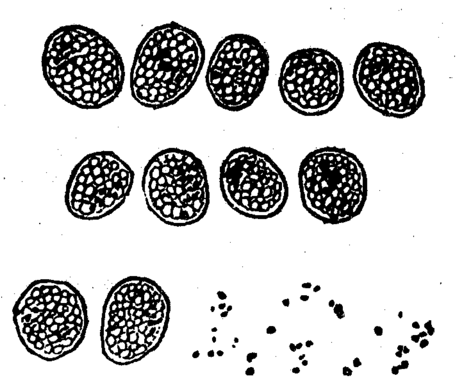
Note on Two Microscopic Preparations of the Mosquitoes by Surgeon-Major John Smyth

Preparation I: A mosquito dissected and mounted seventeen days ago in 40 per cent formalin. The mosquito had been fed five days before dissection on blood containing crescents (These particulars were supplied by Surgeon-Major Ross). I used for the examination a Leitz 1/12 o.g., and Baker's No. 4 eyepiece.

Description: Fragments of air tubes and plumes are conspicuous in the specimen. Here and there are large oval or nearly circular cells containing pigment. There are about twenty of these in the preparation. Taking a field containing about three of these bodies the following would be a description of it, (1) An indistinct groundwork of the altered stomach cells of the insect; (2) A few coils of air tube; and (3) The large pigmented cells referred to above. Taking their major diameters, their size ranges between 0.0187 and 0.0112 mm. They are colourless, faintly granular, present one or two "vacuoles", and have a sharply defined border (a very delicate cell wall or capsule ?). Black pigment granules are found in them, variously arranged, but mostly forming clusters. The number of granules varies from ten to eighteen. In some of them the clustering is nearly or quite central, in others it is marginal. When the latter is the case two or three granules may be seen isolated from the main cluster and arranged in a row along the periphery of the cell. These granules are identical in general appearance with those found in quartan fever; and in *Allbutt's System of Medicine* (1897) the diagrams of the quartan parasite give a very good general idea of the appearances in the specimen I have attempted to describe, the only difference being that the former seem to contain a larger number of granules.

Preparation II: This is a specimen of a mosquito dissected on the fourth day after feeding on blood containing crescents, and prepared on the same date as Preparation I. The only difference observable between this preparation and the other is that the pigmented cells are on the whole slightly smaller, ranging between 0.0175 and 0.0075 mm, and are more hyaline and altogether more delicate in structure.

Surgeon-Major Ronald Ross has been good enough to forward to us the preparations he describes. We have submitted them to Dr. Thin, Mr. Bland Sutton and Dr. Patrick Manson, who report as follows. Dr. Manson writes, "I have examined Surgeon-Major Ross's slides with great interest, and find that his description of the pigmented cells he refers to is accurate. There can be no question that these cells contain a pigment optically indistinguishable from the pigment which is so characteristic a feature in the malaria parasite. The cells are evidently in the wall of the insect's stomach, and are quite different in appearance from any other structure in the preparations. They stand out with remarkable distinctness, the outline of the cell wall, if such it be, being sharply defined, the entire body reminding one of a coccidium-invaded epithelial cell. Until these cells have been stained and their exact structure more carefully studied. It is impossible to say if they contain parasites. Considering the peculiar grouping of the pigment in many instances, a grouping that forcibly recalls what one sees in the living malaria parasite, and the distinctness and regularity of the outlines of the bodies, I am inclined to think that Ross may have found the extra-corporeal phase of malaria. If this be the case, then he has made a discovery of the first importance. It is just possible, however, that these cells may be something quite other than this. Possibly, if they do contain a parasite, it may be that this parasite is not the malaria parasite; possibly these pigmented cells are normal to the species of mosquito he is working with possibly the pigment, though malarial, does not represent a living parasite for, we can conceive that a pigment having been set free in the stomach of the malaria-fed msoquito may be taken up by the cells in the insect's stomach. More work is required before the matter can be finally settled. I have been so impressed by the possibilities of Ross's discovery that I had the accompanying drawings made from his preparations". Mr. Bland Sutton writes, "I



have examined Surgeon-Major Ross's specimens and had an opportunity of discussing the matter with Dr. Manson, and thoroughly endorse his opinion. We must wait until experiments demonstrate the subsequent fate of the intracellular particles before coming to a positive decision. It is a peculiarly interesting and important research, and one which the skill and enthusiasm of Surgeon-Major Ross will doubtless bring to a satisfactory conclusion". Dr. Thin writes, "Dr. Manson has been good enough to show me Surgeon-Major Ross's two specimens. I believe that the objects referred to are epithelial cells, and that the black granules which they contain are pigment derived from the parasite of malaria. (1) *The pigment:* The pigment is found in the form of very minute needles, and in small spheres of varying sizes, but none of them large. This coincides exactly with the forms of pigment observed in the human subject when patients have died of malaria. In the cells of the spleen of patients who have died at Sierra Leone, I found in some of the cells minute needle-shaped pigment; in others both needle-shaped and minute spheres in the same cell, in others only spheres of pigment. By he time the cells have reached the liver the pigment in my cases had all become spherical. Even if I had not known that I was looking at a mosquito's stomach, and that mosquito had been fed on blood containing crescents, the appearances would at once have suggested to me that I was looking at malarial pigment. The position of the pigment in the cells is accurately described by Surgeon-Major Ross. In some of the cells it is irregularly distributed in the periphery, and in others in a small circle towards the centre. There are also small pigment spheres scattered throughout the preparation, without any apparent connection with cells, and the pigment spheres when it was apparently extracellular were somewhat larger than those which were within cells; (2) *The cells:* The cells have the outlines of epithelial cells, and they stand out clearly against the other structures in the preparations. I believe they are the ordinary epithelial cells of the stomach of the mosquito which have undergone change, and for the following reason. I saw the preparations twice. The first time I saw them these cell-like bodies stood out very clearly in a field in which the other elements were very transparent and indistinct. The whole field was covered with minute spherical refractive appearances which seemed to be both outside and inside the cells. Before I examined the preparations the second time some change had taken place (probably by the introduction of cedar oil under the edge) which caused all the tissues to refract the light more strongly. The result was to render them much more favourable for observation. The numerous minute spherical particles no longer arrested the attention. The bodies in question were, as before, more distinct than anything else in the field, but in addition a number of other cells of the same size and general shape had come into view, presenting the ordinary appearances of epithelial cells, and in many of them the nucleus was distinct. On closer observation it was seen that the epithelial cells were arranged in rows in contact with each other, and that in some of them minute needles or spheres of pigment were present, and that the cells in which pigment was present stood out more distinctly than those which did not contain pigment. No doubt was, therefore, left in my mind that the bodies in question were the ordinary epithelial cells of the mosquito's stomach containing malarial pigment, and it became evident to me that when one of the epithelial cells of the stomach is infected with malarial pigment it undergoes changes– I have no doubt of a destructive or *post-mortem* character– which alter the refractive character of the cell, and make it stand clearly out on a transparent background. The small circles of pigment which are to be seen in some of these bodies are so arranged as to render it almost certain that they are arranged round the nucleus of the epithelial cell. I found in the Sierra Leone cases, in the large white cells of the spleen that were not much infected by pigment, that the pigment was first found in the outer part as fine needles, and afterwards was grouped in spheres round the nucleus. How can we account for the infected cells standing out so much more clearly than the unaffected cells? I consider this to be analogous to what takes place in the endothelium of the blood vessels in the capillaries of the brain, spleen and liver in the Sierra Leone cases. The endothelial cells of the capillaries which contain pigment– and many of them do contain pigment– swell and become altered in their substance, shown by their taking up an eosin or cochineal stain when the healthy cells that do not contain pigment do not stain. In the human subject these infected endothelial cells are doomed to destruction. All this was described in the paper which I read at the Royal Medical and Chirurgical Society on October 26th, and illustrated by microscopical preparations. Reasoning from analogy, I infer that the epithelial cells in the mosquito's stomach that absorb pigment are injured by the pigment, are altered by it, and would eventually be killed by it, and that the injured or dead cell possesses different refractive qualities from a living and uninjured cell, and stands out clearly in an otherwise almost transparent field. It is quite natural to expect that if a mosquito is fed on blood containing crescents, the pigment of these crescents should be found, after the crescent have been destroyed, in or about the stomach of the insect, and as animal cells possess the property of taking up very minute granules (the liver cells as well as the capillary endothelium take up pigment), it is reasonable to infer that they might be found in the cells of the stomach of the mosquito. What is to me extraordinary about the matter, and requires further explanation, is why this appearance is found only in one species of mosquito. I see no trace of the parasite of malaria itself in these preparations, but, as they are unstained, it does not necessarily follow that it is not there. It will be evident, from what I have remarked, that I consider that these appearances do not represent parasites, and that the extra-corporeal stage of the parasite of malariae which Koch and Pfeiffer were, I believe, the first to suggest might be found in the mosquito, has not yet been observed, for so far, all the changes in the form of the crescent, and in the throwing out of flagella, which take place in the mosquito's stomach, can be produced at will (as has been shown by my friend Dr. Marshall, and afterwards verified by Dr. Manson), by the simple addition of distilled water. Although I have not been able to satisfy myself that these preparation show any development of the parasite of malaria in the mosquito's stomach, I hope it will not be considered that I undervalue the great importance of Surgeon-Major Ross's investigations. His published papers, and not the least them to which this note is appended, show that he is a patient, skilfull, and indefatigable observer. He has already added considerably to our knowledge of the mosquito and its parasite and after what has been ascertained of the association of the mosquito with the filaria sanguinis hominis (in connection with which Dr. Manson's name is so distinguished), no one can believe that any information regarding the parasites of the mosquito may not turn out to be of great practical value, as it certainly is of considerable scientific interest. It is therefore, I consider, very important that Surgeon-Major Ross, with his exceptional capacity and opportunities should continue his investigations not only regarding the mosquito in connection with the parasite of malaria, but also by working in any other lines which his observations point out to him as possibly leading to a solution of the unsolved riddle of the existence of the parasite outside the human body, for outside the human body we know it does and must exist. It is a subject of congratulation to everyone interested in the welfare of India, and indeed in that of the whole tropical world, that men like Surgeon-Major Ross should be found willing to devote themselves to this difficult and fatiguing work. Only men endowed with unusual enthusiasm could be found to devote themselves as he has done to such a task. In the interests of science it is therefore most desirable that support, assistance if required, and every facility should be given to him to enable him to continue his researches.

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Ronald Ross and India

MARY E. GIBSON

The life of Ronald Ross in India, and the background to his proving that mosquitoes carry malaria, is described.

Keywords: India, Malaria, Mosquito, Ronald Ross

Although Ronald Ross was born in India at Almora in May 1857, like most British children of his time, he was sent home for his health and education just before his eighth birthday. He returned in 1881, having qualified as a Member of the Royal College of Surgeons and a Licentiate of the Society of Apothecaries, as a newly Commissioned Officer in the Madras Presidency section of the Indian Medical Service.

Ross arrived in Bombay towards the end of October 1881 and travelled by train, a journey of three days, to Madras where he was posted to the Station Hospital[1]. His duties were negligible and promotion was slow as the junior ranks of the Indian Medical Service were overfilled. His life was leisurely and, after taking a necessary examination in Hindustani, he filled his time with studying literature until he was given temporary medical charge of the 10th Madras Infantry which was stationed near Bangalore. There he passed his ample spare time exploring the countryside on foot while composing poetry, and shooting, although he admitted that he was a poor shot. It was in Bangalore two years later that Ross tried his first experiment in mosquito control by overturning a tub of water outside his window in which he discovered mosquito larvae. He met his first official rebuff for his investigations when he was rebuked by the adjutant who held that mosquitoes were in this world for a purpose and that trying to prevent their breeding was an

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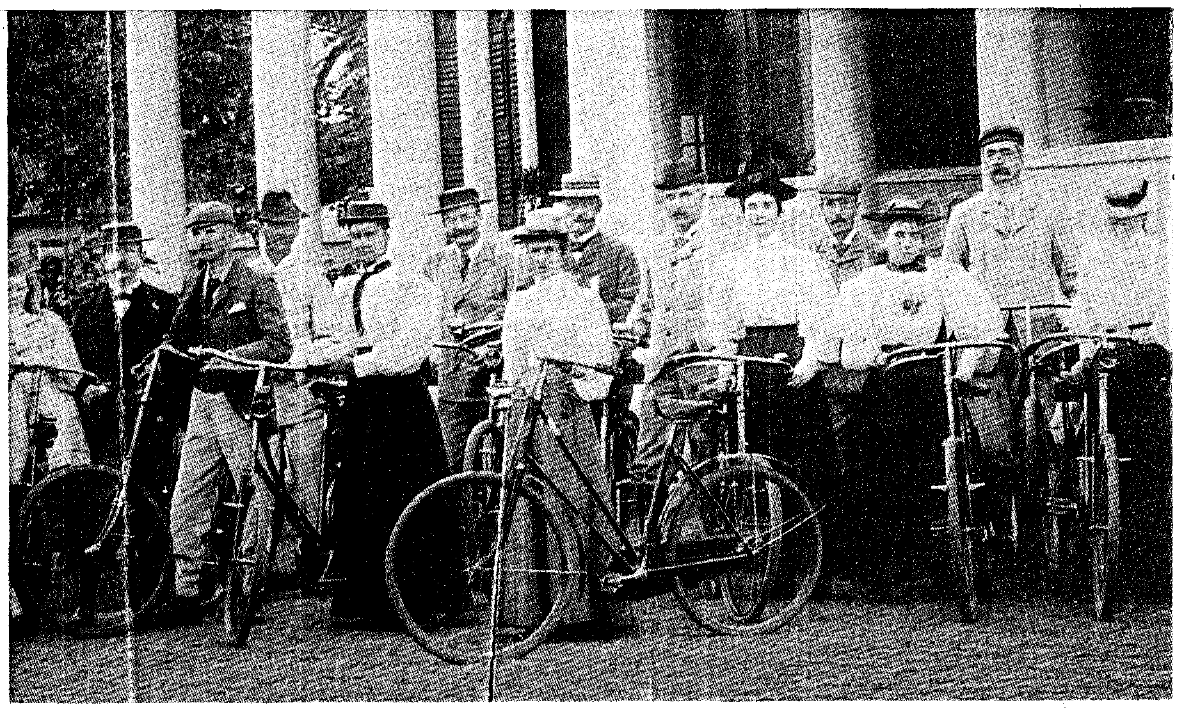


Ronald and Rosa Ross at a meeting of the Bangalore Bicycle Club c. 1895. Mrs. Ross is in the middle with a bicycle in front of her and Ronald Ross is immediately behind her.

abuse of nature[2]. After a year in India Ross was inspired to add the study of mathematics to his interests but apart from these solitary pursuits his life appears to have been similar to most young officers in the Indian Medical Service with occasional attachments to various regiments and abundant spare time. Officers were supposed to have a year's home leave every five years but Ross only obtained his after seven years by threatening to resign if he were not given the furlough due to him[3].

During this furlough Ross studied for and gained the Diploma in Public Health and obtained an extension of two months to his leave in order to study bacteriology under Professor E.E. Klein[4]. He maintained that he was the first Indian Medical Service Officer to undertake either of these actions.

He returned to India with a bride and a a box of bacterial type-cultures and was immediately posted to Burma leaving his shy wife in a hotel in Madras. After a month she was allowed to follow him but while he escorted columns of sick and wounded through Burma she had to remain in Pakoko.

After six months Ross returned with his wife to Madras where he was given a three year posting as Staff Surgeon at Bangalore. Here Ross decided to take an interest in malaria as most of the fevers in Bangalore were attributed to it although he said that many were enteric. Although he knew of Laveran's discovery of *Plasmodia* he had been unable to find them in blood samples and was of the opinion that malaria was also an enteric complaint which he called 'enteroseptic fever', writing articles in support of his thesis[5,6]. He was still writing poetry and fiction, and also returned to mathematics.

The appointment in Bangalore came to an end in April 1893 and, after three months leave in Coonoor, Ross was given another temporary posting as Medical Officer with the 20th Madras Infantry and then a permanent one to the 19th Madras Infantry at Berhampur. In February 1894 he and his family, which now included two daughters, sailed for leave in England. During this period Ross was advised by Professor A.A. Kanthack, the pathologist at St. Bartholomew's Hospital, to visit Patrick Manson. Manson demonstrated *Plasmodia* to Ross, convincing him that they were the cause of malaria, and Ross was awarded the Parkes Memorial Gold Medal by the Army Medical Service for an essay on the subject[7]. Manson had discovered that mosquitoes were the vectors of filariasis[8], although he was unaware of the complete life-cycle of filaria, and he hypothesized that they also carried malaria[9]. Ross returned to India in March 1895, fired by Manson's enthusiasm, leaving his wife and family which had now been augmented by a son, to follow him.

Ronald Ross, c. 1894

Ross had designed a portable microscope, which was made up for him by the firm of Charles Baker, and he whiled away his journey by searching for parasites in the shipboard cockroaches and fish that he caught. He also started his regular correspondence with Patrick Manson which continued until his return to England in 1899. The first letter was written on board but was lost before Ross wrote his autobiography.

When he arrived in Bombay he was delayed for two days and spent them in trying to find malaria parasites in cases in the Civil Hospital before travelling on the rejoin his regiment in Secunderabad. He complained to Manson about the amount of work he found waiting for him but still managed to spend four days of his first week back looking down a microscope to search for *Plasmodia*, discovering them in five out of eleven cases— again in the Civil Hospital as the military patients had been 'drenched with quinine'.

He had hopes of being employed to investigate malaria as Surgeon-Major Charles Owne, the Medical Advisor to the Maharaja of Patiala, had persuaded the Maharaja to apply for Ross's services but the Punjab Government refused the application on financial grounds. They may have also been unwilling to obtain a secondment for a officer from another presidency. Ross's eagerness to obtain official support was causing trouble for him with his superiors in Madras and he received a reprimand for not applying for a transfer to the Civil Medical Department through the proper channels.

At first Ross wrote to Manson at approximately weekly intervals giving details of his experiments but later there were sometimes longer gaps. He described the results of his experiments in early June, of how he had given water, in which mosquitoes had died, to a man called Lutchman, who maintained he had never had malaria. Ross's hopes rose with Lutchman's temperature but both subsided after three days without Ross's finding any parasites in Lutchman's blood samples.

Ross had observed exflagellation but neither he nor Manson were aware of its significance. Manson believed that the parasite might be transmitted from mother to daughter in a somewhat similar fashion to ticks acting as vectors of Rocky Mountain spotted fever[10,11] or that the passage was enteric through ingestion of infected dust. Ross favoured the enteric passage.

He was having problems in finding cases of malaria and warned Manson not to mention that Lutchman was a doolie-bearer employed by the government as he was not supposed to use government employees for his experiments. At the same time Ross had been told that the suggestion of a Patiala malaria inquiry had finally been abandoned because the Lieutenant-Governor of the Punjab was implacably opposed to the idea and he applied for a transfer to the Civil branch of the Madras Service. In London, Manson was writing to Ross's superiors in the Indian Medical Service on his behalf. This probably did nothing to endear Ross to them.

In default of malaria cases on which to feed his mosquitoes Ross studied them intensively to discover what parasites they harboured[12] and thought that the psorosperms he found in them might prove to be material to the transmission of malaria.

At the beginning of September 1895 Ross was suddenly transferred to Bangalore to deal with an epidemic of cholera. Looking back on this interruption to his malaria work when he came to write his autobiography Ross perceived it as a blessing in disguise "It gave me an almost unique experience in practical sanitation which was invaluable when we came after 1898 to apply *the* proved mosquito-malaria theory for the benefit of suffering humanity"[13]. The attitude of the authorities can be gauged by a letter from Colonel J.T.W. Leslie, then Secretary to the Director-General of the Indian Medical Service and subsequently himself Director-General, asking for "a brief account of your experience of the malaria parasite in India", and if Ross had been successful in controlling cholera in Bangalore after arriving ten days previously.

Ross said it took him five weeks to control the epidemic and he submitted his report and recommendations to the British Resident in January 1896[14]. He was immediately appointed to carry out his own suggestions and when A.F. Dobson, the Residency Surgeon went on leave at the end of May 1896 Ross became Officiating Residency Surgeon and remained there for a further year[15]. Ross's measures, which included the imposition of a 'cess tax' were not popular with the local populace, both Indian and British. Some of the newspapers, such as the *Madras Mail* and the *Daily Post*, were in favour of his reforms while others, such as the *Evening Mail*, violently opposed them. However, with the support of the Resident, he enforced his sanitary measures and left Bangalore with an official commendation[16].

During this period at Bangalore Ross continued to work on malaria and report regularly to Manson in London. On 27 May he said that he had noticed that mosquitoes injected saliva when they bit and speculated that malaria might be transmitted by this method and in his next letter which was written four months later he remarked that flagellation did not occur in every species of mosquito. Manson was sceptical about the transmission of malaria by mosquito bite because he thought they only bit once in their lives.

Towards the end of 1896 Ross applied to be put on special duty to investigate malaria when his posting at Bangalore ended and he told Manson that he was optimistic about the outcome. He also suggested that not all species of mosquito carried malaria. Ross sent a paper on ex-flagellation to the *British Medical Journal*, which was published in January 1897[17], and was confident that as it was published with an addendum by Manson it would ensure an official investigation. He also wrote an anonymous article in *The Pioneer* calling for an official investigation into malaria[18], but his stay at Bangalore came to an end in March 1897 without his hearing anything definite, although Manson had written to Surgeon-General James Cleghorn, Director-General of the Indian Medical Service. Ross had also managed to enlist the support of the United Planters' Association, a member of the Madras Executive Council, the Civil Surgeon-General at Madras, Charles Sibthorpe, and the Sanitary Commissioner at Madras, Surgeon-Colonel Walter King who had all written to the government in Shimla urging an official inquiry into malaria[19].

Ross applied for and was grudgingly granted two months privilege leave at

Ootacamund where he was told to await further orders. It was there that he eventually learnt, after he had turned down the offer of a more lucrative posting[20] and had been snubbed when he applied for the post of District Medical and Sanitary Officer at Ootacamund, that the malaria enquiry had been shelved. Ross told Manson that the Indian Government was dubious about the inquiry because they were thinking about setting up an institute of public health. He resolved to spend his leave at Ootacamund investigating malaria in a notoriously unhealthy spot called Kalhutti at the bottom of Sigur Ghat. It justified its reputation since Ross developed malaria after three days, despite sleeping under a mosquito net, and had to return to Ootacamund to recover. When he went back to Sigur Ghat mosquitoes were few although many people had enlarged spleens or fever. It was here that Ross had his attention drawn to *Anopheles*[21], but he did not realise its significance and continued to investigate the parasites of the more obvious *Culex*[22] until his leave ended in mid-June 1897 and he returned deeply discouraged to his regiment at Secunderabad, leaving his family in Ootacamund[23].

No sooner had Ross rejoined his regiment than there was a regimental guest-night followed by an outbreak of cholera among the participants. Ross was one of those afflicted and treated himself by drinking "hot tea without milk or sugar to maintain the water-content and the pressure of the blood"[24]. After his recovery Ross suffered further humiliation at the hands of Surgeon-Colonel Edward Lawrie, who did not believe in the existence of the malaria parasite. Lawrie invited Ross to demonstrate it to the staff and students of the Nizam's Medical School at Chudderghat and early one morning Ross sent a patient, who had an early infection with *Plasmodium falciparum*, following himself later in the day. Much to his embarrassment when he endeavoured to display them he could find no parasites in the man's blood as they had all disappeared. He said that he was aware of this phenomenon but did not think that it would happen so quickly. He was so ashamed of this episode that there is no mention of it in his correspondence with Manson although he does relate the story in his *Memoirs*[25].

Ross was still trying to obtain an exchange to a more lucrative post and had received encouraging replies to his applications from Colonel J.T.W. Leslie. Manson had written to Sir Charles Crosthwaite, a Member of the Council of India in the India Office in London saying that Ross was in the lead in the race to discover the method of transmission in malaria but his prospects in the Indian Medical Service were so poor that he would probably retire and return to Britain. Crosthwaite was supportive but Manson warned Ross that he had been told that the Director-General of the Indian Medical Service would resent outside interference on Ross's behalf. Manson also approached the Viceroy and the Secretary of State but later events indicated that all this activity may have been counter-productive.

Ross persisted in his dissection of mosquitoes but the only ones that were available were *Culex*. He was suffering considerable discomfort from the heat because he could not use the *punkha* as the current of air blew away his partially dissected mosquitoes[26]. However, in mid-August his luck changed when one of the men whom he employed to catch mosquitoes brought him some eggs which differed from the usual ones. The following day, 16th August, one of his assistant pointed out a different species of mosquito sitting on a wall which he caught, dissected "and found nothing unusual"[27]. While Ross was doing this the same Hospital Assistant ran in to tell him that the different eggs had hatched into mosquitoes similar to the one he was dissecting. They were fed on a malarious patient, Husein Khan, but no changes were found in them on August 17.

Unfortunately for Ross his mosquito catchers could not find any more eggs of the mosquitoes that he called "dappled-winged" and by the 19 August he had only three left. One of those died in the night and when he dissected it on the 20th there was nothing unusual to be seen. He killed his last but one of the batch that had hatched and been fed on the 16th and found nothing until he examined the stomach where he at once found some strange cells which contained black granules. He made notes of his findings and drew rough sketches as well as sealing his specimen and the following day returned to the laboratory, killed his last mosquito and dissected it, finding similar but larger cells[28].

Two days later Ross wrote to Manson describing what he had seen but adding that he could find no more 'brown mosquitoes'. He had examined some *Stegomyia* which had been fed on malarial blood, paying special attention to the stomach but found nothing. The next day he managed to catch a few wild 'brown' ones but could not find similar cells in them. Ross intended to send his specimens to Manson but before he did so he received a letter from Manson warning him that previous specimens had deteriorated *en route*. He therefore kept them but wrote a brief article for the *British Medical Journal* with corroboration of his findings from a colleague, Surgeon-Major John Smyth[29]. In the Indian Medical Service it was customary to send one officer to check on research work done by another and Ross probably decided to ask a friend to support his findings rather than wait for someone who might be antagonistic towards him and the mosquito-malaria theory. Ross said that the article was posted at the beginning of September but it did not appear in print until the middle of the December. He also wrote a full report for the Director-General of the Indian Medical Service which he dispatched 'through the proper channels'. However, before he did this he had written to J.P. Hewitt, the Secretary to the Home Department of the Government of India with a letter of introduction from Sir Charles Crosthwaite, provided by Manson, asking for news of the malaria inquiry, adding that his prospects were so poor that he would have to apply for his pension at the first opportunity.

Ross discovered that the 'brown mosquitoes', i.e. *Anopheles* bred in puddles and was able to collect some larvae. Three died but he succeeded in feeding the sole survivor on a case of malaria and dissected it two days later and found similar but smaller pigmented cells. He was overjoyed and convinced that all he had to do was to spend another fortnight on his research before the problem was finally solved[30].

At this point his efforts to obtain a different posting would appear to have borne unexpected and bitter fruit. On the 23 September Ross received orders to report immediately to the Principal Medical Officer, Bombay for military duty. In response to a flurry of telegrams the Madras Principal Medical Officer's Secretary said that he might have to accompany a field hospital, but he also received a reply from the Principal Medical Officer in Bombay saying that nothing was known there of his posting.

On 27 September Ross wrote to Manson from Bombay to tell him of the interruption to his malaria work and to report his progress to date. The local Principal Medical Officer had no idea why Ross had been sent to him but, after making inquiries, discovered that Ross was being posted to a place called Kherwara in Rajputana. Ross was delighted because he thought it would be a suitable place to continue his malaria work and that his wife and children would able to join him[31], but his hopes were quickly dashed. He had great problems in reaching the place and the journey involved not only a prolonged railway trip but also a lengthy *tonga* ride. When he arrived he was told that there had not been a case of malaria for months and the work was minimal. In a footnote in his *Memoirs* Ross said that he assumed that on receiving his report about pigmented cells the Principal Medical Officer at Madras said "Here is this fool writing about mosquitoes again: let us give him a change of scene"[32]. It would appear that Ross's efforts to move and the high powered support he had enlisted had offended his superior officers.

Initially he was optimistic because he wrote to Manson that although the post at Kherwara was a military appointment worse than the one he had left he assumed that he was sent there as an alternative to going to the front and that he should return to Bangalore as soon as his temporary posting ended. He also hoped that D.C. Johnston, the Medical Officer of the Meywar Bhil Corps, whom he was replacing, would soon be sufficiently recovered from dysentery to resume his duty but Johnston said that he had a relapse and was applying for home leave. Ross noted acidly that he had piles.

Some of the Indian Princes were trying to form a Northern Indian Health Institute and Ross applied for a post there through Surgeon-Major Charles Owen who initially was encouraging but later expressed doubts about the mosquito-malaria theory as he was afraid that if it were a false trial it would affect the reputation of any establishment with which Ross was connected. He also kept warning Ross not to publish his work precipitately. From the correspondence it would appear that Owen was warned against support for Ross and did not wish to commit himself before Ross's discovery was incontrovertibly proved.

Manson also warned Ross that it was unwise to persist in pestering senior civil servants at the India Office and that would have to wait.

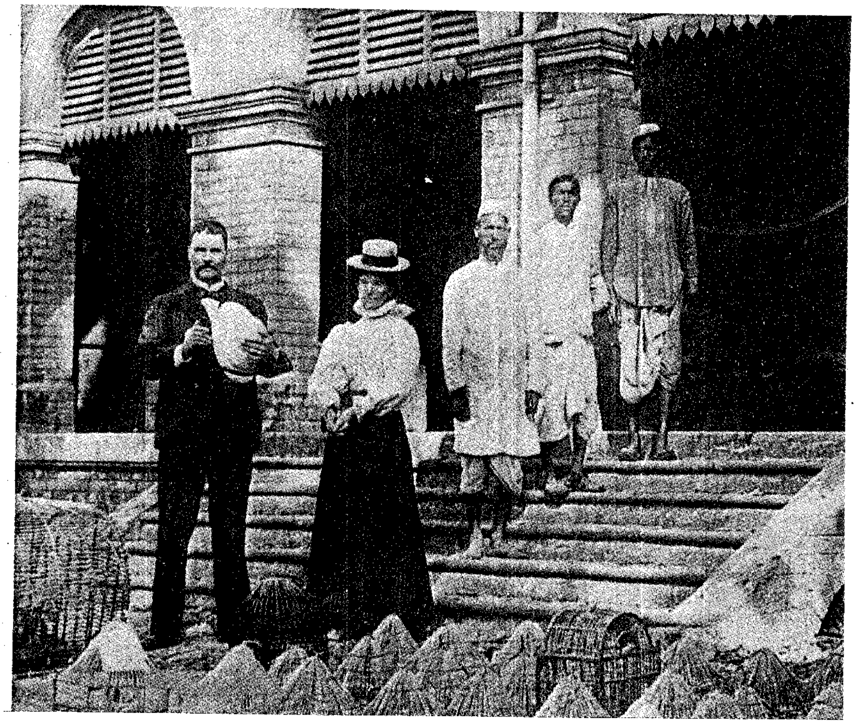
Despite his pleas and the support of his Commanding Officer at Kherwara, Ross was not allowed to leave even briefly in order to provide suitable accommodation for his family whom he had left in a hotel, his applications for other posts were either refused or ignored and he became very depressed and again threatened to resign at the first opportunity.

While at Kherwara he wrote a further paper on the pigmented cells[33] and investigated the parasites of birds and their possible vectors but did not find any pigmented cells. As the weather got warmer he found 'brindled' mosquitoes breeding in pots of water round his house but after examining them thoroughly after feeding them on a case of quartan fever found no pigmented cells.

Manson was still pressing for Ross to be put on special duty to research malaria, but the Director-General of the Indian Medical Service said that he could not over-ride the orders of the Principal Medical Officer, Madras, who was not prepared to second his officers during a plague scare and a campaign on the Northwest Frontier.

At the end of January 1898 Manson's efforts were at last successful and Ross received a telegram from the Director-General of the Indian Medical Service saying that the Government had sanctioned his going on special duty to investigate malaria and it was followed ten days later by orders to go to Calcutta for civil employment.

When Ross arrived in Calcutta he discovered that an earlier suggestion that he should also investigate *kala-azar* had been added to his six months malaria investigation. However, he was also told that if necessary he could apply for an extension of a further six months when the original period came to an end. Ross discovered that the laboratory in Calcutta was 'swarming' with the mosquitoes that were so difficult to find elsewhere. He continued to work on avian parasites and hired men to bring him birds to work on as his work on human malaria was being frustrated by the unusually low temperature and the paucity of suitable cases of malaria. He asked for permission to travel

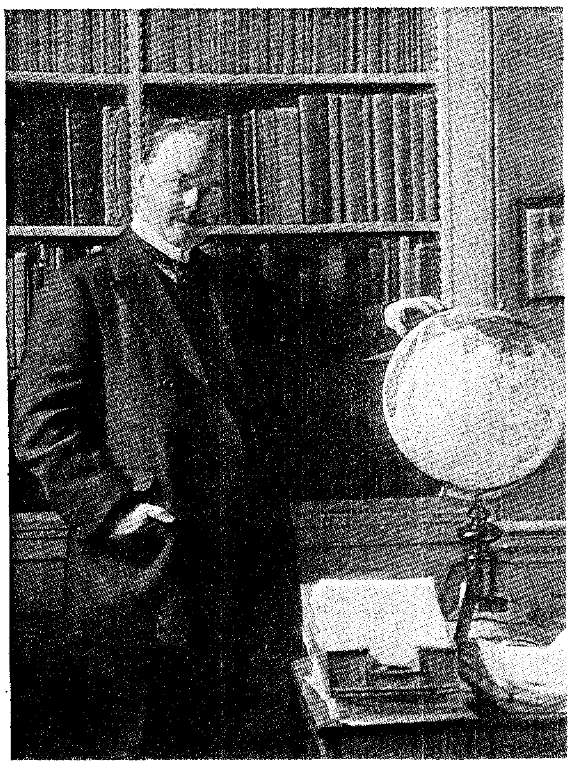


Ronald and Rosa Ross with his assistants, includ-ing Mahomed Bux, on the steps of his laboratory, Calcutta, 1898.

to more malarious places than Calcutta but was told that this would have to be sanctioned by the Government of India.

A week later he wrote to Manson in great excitement. He had discovered that he could produce pigmented cells at will by feeding 'grey mosquitoes on larks infected with proteosoma', while those fed on uninfected birds did not produce the characteristic cells. He continued to give Manson details of his work but had to stop in mid-April to write an interim report for the Director-General on which depended the success of his application for an extension of his special duty[34]. He also

Ronald Ross with his microscope, Darjeeling 1898.



Ronald Ross, 1913.

The local populace were convinced that he was trying to inoculate them with plague and the local planters begged him to stop taking blood samples because their workers were fleeing in terror.

Ross posted his interim report[35] to J.T.W. Leslie, Secretary to the Director-General of the Indian Medical Service on 24 May and applied unofficially for an extension to his special duty and a commissioned assistant the following day. He was told that he could not publish his report until his work had been confirmed by others nor could he have an assistant. He was allowed to have the report printed for private

Ronald Ross, c. 1915.

obtained ten days leave which he spent with his family in Darjeeling and, having obtained permission to visit the Terai, made his temporary headquarters at Kurseong between Darjeeling and the Terai. Here he was frustrated in his efforts by the local birds being free of parasites while the ones that he had brought from Calcutta had died.

He was worried by the thought of having to include *kala-azar* in his research. He found patients with 'Terai fever' were infected with such a variety of parasites that it was difficult to say which one predominated and he thought that *kala-azar* would present a similar condition. He also had a plague scare to contend with.

distribution and it was ready by the beginning of July.

Ross asked for and was given permission to return to Calcutta at the end of May where he continued to work on the zygotes which he found in mosquitoes infected with avian malaria. He was not allowed to use human patients because of the plague scare.

Toward the end of June he finally discovered what happened to the zygotes.

Ronald Ross, 1930.

Ronald Ross, c. 1915.

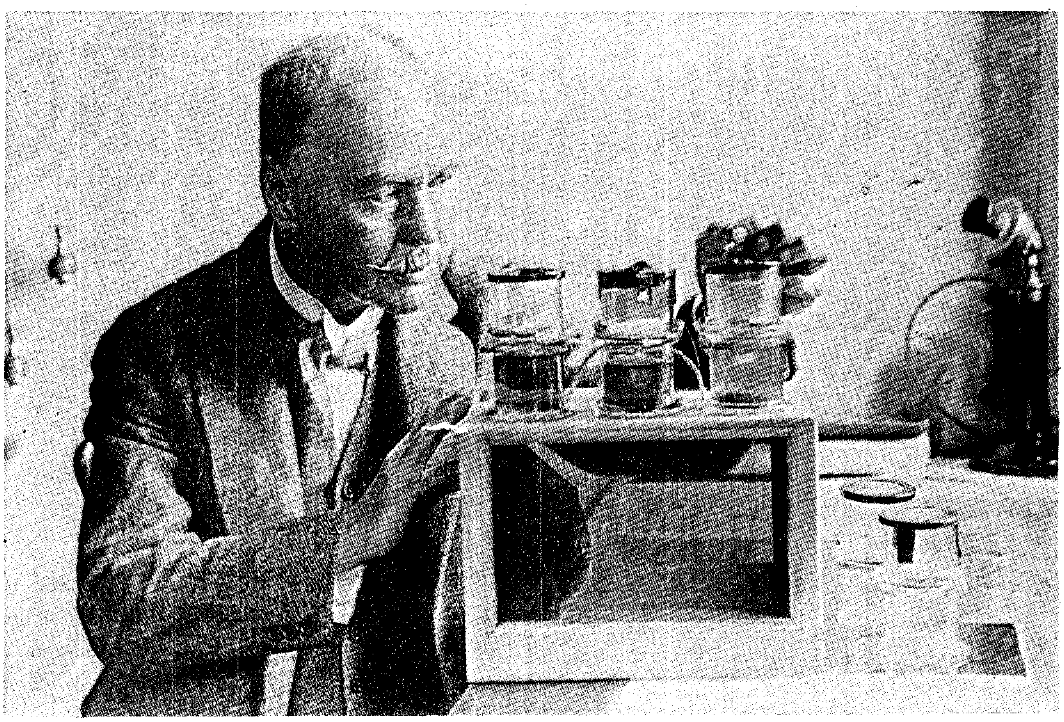
He found that the cells in the mosquitoes' stomach contained what he called 'germinal threads' or sporozoites which penetrated the stomach wall. At the beginning of July he achieved his goal, finding that they congregated in the salivary gland of the mosquito and were injected when it bit. He confirmed this by infecting healthy birds through the bites of mosquitoes. His specimens, report and letters reached Manson in time for the Annual Meeting of the British Medical Association in Edinburgh at the end of July and Manson, who was in great pain with gout, rose from his bed to make the announcement of Ross's success to the Tropical Diseases' Section.

By this time Ross's work had attracted the support of Alphonse Laveran and Lord Lister, then President of the Royal Society, and Manson persuaded the Royal Society to send Dr. Charles W. Daniels to work under Ross to gain experience, although his suggestions that there should a commission to thoroughly investigate malaria came to nothing[36].

Ross was granted a six month extension to his special duty but was not released from the obligation to work on *kala-azar*, for which he had hoped. A month later he was told that there was no guarantee that he would be able to continue on research work and advised not to make further applications to do so. He was also denied permission to publish his report on *Proteosoma* until the end of September 1898.

Like several others who had worked on *kala-azar* Ross was convinced that it was a form of malaria, which was not surprising as most of the patients had malaria parasites in their blood[37]. He spent three months investigating *kala-azar*, firstly at Kurseong and then at Nowgong in Assam, returning to Calcutta in mid-November 1898 to write his report — against background noise of tin packing cases being hammered into shape next door.

In his *Memoirs* Ross complained that few of his colleagues in the Indian Medical Service came to look at his work but Dr. Sidney W. Rivenburg, from the



Ronald Ross, 1926.

American Mission in Assam, came to Calcutta to learn his techniques and C.W. Daniels arrived as an emissary from the Royal Society. Ross said that he was "polite but cold" and initially dubious about Ross's findings, but was quickly convinced of their authenticity[38]. He later provided Ross with a written statement confirming Ross's demonstrations to him and his priority in making them although Ross never published his observations. Ross was also visited by Dr. Almroth Wright, then Professor of Pathology at the Royal Army Medical College, and Dr. March Armand Ruffer, who were already visiting India. Ross was convinced that they were sent to spy on him[39].

Ross struggled with his report on *kala-azar* which was submitted to the Director-General at the end of January 1899[40]. He was then allowed six months leave with a vague promise that he might be allowed to continue research if the Government of India approved. However, Ross told Manson that he intended to retire at the end of his leave and would not return to India without the inducement of "hard cash". Ross left India on the 22 February 1899 and, as he had threatened, handed in his resignation from the Indian Medical Service. It was ten years before he returned to the 1909 Bombay Medical Congress. Then he was an honoured guest who was entertained during his visit by the Governor, Sir George Sydenham, but his ideas on mosquito control were denigrated by some of the delegates[41].

In January 1927 he made his final visit to India, when the "Gate of Commemoration" in Calcutta was unveiled by Lord Lytton. He also visited tea plantations in Assam and around Darjeeling but the trip was primarily a fund raising trip in aid of the Ross Institute which had been formally opened in July 1926.

In the autumn of 1927 Ross had a stroke which confined him to a wheelchair until his death in September 1932, rendering further visits to India impossible.

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The Intellectual Legacies of Ronald Ross

DAVID J. BRADLEY

INTRODUCTION

Ross was not only a genius but a many-sided genius, and his restless intellect roamed over diverse fields, making contributions to all, but of very uneven quality. His purely literary and his musical output is beyond the theme of this paper, and way beyond the competence of this writer, to address, but within the natural sciences and mathematics Ross's published work follows several themes but with strong inter-linking bridges, and that which bears a relationship to communicable diseases, above all malaria, forms a massive and coherent body of work. Indeed, it is a pity that Ross expended so much time and energy on inter-personal quarrelling and peripheral scientific efforts, as otherwise he could readily have done for all of communicable disease epidemiology what he achieved for malaria.

Because of his egocentric and somewhat abrasive character, Ross created no group of researchers around him; he was essentially a 'loner'. But his intellectual positions were directly transmitted into the Ross Institute through Malcolm Watson and continued thereafter. Moreover his thinking and the positions he took over malaria control have influenced the field up to the present. They have become transformed along the way, as do all intellectual legacies of value, and here I trace the modes of thought about public health – what he would have called sanitary problems – and their relevance to today as well as his work on malaria and related issues. This paper emphasizes the issues and Ross's work on them, without addressing in detail the questions of precisely how far Ross was the first to formulate them. Discussion of great discoveries has been obscured too often, and especially in the cases of malaria and of HIV, by fruitless and demeaning arguments about priority, to which this paper does not wish to contribute. Rather, there are several fields where

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Ross, either by his originality, or by his clarity of analytical thought, or by his trenchant attributes, has made a decisive contribution that continues in an evolved form today.

Malaria Life Cycle

The work on the malaria parasite life cycle, which we celebrate today so rightly and happily, and for which Ross received such justified acclaim during his lifetime, perhaps needs least comment in this paper. It is a familiar story and the outlines of it are both romantic and substantially true — the scientist working away, with little support from his employers, persevering through difficulties and disappointments to eventually show that the malaria parasites develop on the stomach wall of the mosquito. The stimulus to begin and the constant support and encouragement of Patrick Manson counted for much in this phase of the work.

It is perhaps remarkable that Ross turned to biomedical research relatively late. He studied both bacteriology and public health after the age of 30 years, made some desultory attempts at minor research studies soon after, but did not settle to laboratory-based research until he was inspired by Manson at the age of 37. The mosquito day discovery was therefore the result of $2^{1}/_{2}$ years of intensive research, pursuing all available avenues of study, from attempts at infection of people experimentally to investigation of the protozoa found in mosquitoes. The amount of work done was indeed impressive, when one realises that during this period he also had to go and control a cholera outbreak in Bangalore and that he had an attack of malaria himself.

The nature of his first success is known to all – that malaria parasite can develop in some sorts of mosquito (dappled-winged), giving rise to "coccidia" on the stomach wall.

The more original aspect of his research, during 1898, concerned the subsequent fate of the parasites. This had not been predicted by Manson, though Bignami in Italy had accurate ideas about this second phase but mistaken ones about the earlier part of the cycle. As is again well known, Ross now had to work with bird malaria because of the scarcity of human cases, but he successfully showed that the parasites migrated to the salivary glands of the mosquitoes and that such infected mosquitoes could pass on the malaria to healthy birds. He came as near to fulfilling Koch's postulates as was possible prior to Trager's cultivation of *Plasmodium* over half a century later.

His great achievement was to have closed the cycle – to have shown that what happened in the dappled-winged mosquito was adequate to explain all of malaria outside the vertebrate host. In spite of the earlier work of Manson on filaria, which was incomplete so far as transmission back to man was concerned, and of Smith and Kilborne[1] on Texas fever of cattle that is transmitted by ticks, it was Ross's work on malaria that firmly established the concept of vector-borne diseases of people, where there is an alteration between a vertebrate host and an arthropod, more particularly between man and insect.

So, Ross's first legacy is that of insect borne disease, with a necessary part of the parasite life cycle taking place in each of the two alternating hosts. This was immediately extended from bird malaria to human malaria by the Italian workers, and of course has been the mainstay of parasitological research until a couple of decades ago. The dramatic change in perception of tropical disease transmission is easily seen by reading the first edition of Manson's *Tropical Diseases*, published in 1898, where the results of Ross's work are just emerging but where the accounts of plague, leishmaniasis, and the other vector-borne diseases have a vagueness rapidly to be dispelled in the later editions.

But if 1894 saw the beginnings of Ross's parasitological work, the end of the century saw its virtual completion. The great malaria problem had been solved, and Ross was emphatically not an obsessive parasitologist. He made a few minor contributions during the next decade, chiefly in development of his thick film method of examining blood from the mosquito stomach for malaria parasites, but otherwise the microscope on his desk remained symbolic and for teaching. He had solved the key problem, and his other main contributions were in relation to the application of his discoveries.

A Rational Epidemiology

Whilst it is risky to indulge in might-have-beens, it seems likely that if Ross had never entered malaria research other workers would have solved the riddle of transmission within the succeeding five years. Probably the Italian workers would have made the discoveries by then.

However, in other fields of work, Ross's originality is more striking in that others were even slower to pick up on his ideas. Ross, in the years before he met Manson, in the leisure generated for a soldier in times of peace and after writing diverse plays, novels and poems, applied himself to mathematics at the age of 25 years and clearly had a bent for it, both pure and applied to practical problems. In the parasitological research years, he reverted to mathematics to assess the consequences of proximity to water bodies if the mosquito theory were true, applying the inverse square law to show that a nearby puddle may be as dangerous as a more distant large marsh. His reasoning sufficiently impressed Manson that it is quoted at length in Manson's *Tropical Diseases*.

Following the great discovery of mosquito transmission of malaria, Ross at once went on to suggest that if mosquitoes transmit malaria, control of mosquitoes might be expected to control malaria. There was a striking difference in acceptance of these two ideas. His work on transmission was clear, rapidly accepted, and soon confirmed by many.

The approach to disease control by mosquito control was widely derided and received little acceptance at first. Key grounds for rejection were that areas cleared of mosquito breeding would be rapidly reinvaded from beyond, and that to get rid of every anopheline mosquito from an area was a hopeless endeavour. Prior to having evidence from the field, Ross turned to mathematics in order to defend his position, again using the inverse square law, in the form of the 'drunkard's walk', to explain that the likely distance and degree of re-invasions from outside would not vitiate attempts at control.

To deal with the other objection to vector control, Ross constructed an epidemiological model of transmission and was able to show that it was unnecessary to get rid of the last mosquito, that if mosquito density were reduced below a threshold level the rate of getting new infections would fall below the rate at which infected people recover, so that the malaria would gradually die away. This 'threshold' theory has stood the test of time well.

Ross developed this work in detail in his report on malaria control in Mauritius, and, more accessibly, in the great work which he edited, and largely wrote, on the prevention of malaria. It is remarkable as a public health book of any period, and especially for its time, because of its rigorous and quantitative analytical approach. This marks the start of Ross's second major legacy, a rational and quantitative approach to communicable disease epidemiology.

He had three aspects of his work to offer. First is the overall conceptual approach. He distinguishes clearly between 'deductive' and 'constructive' epidemiology. The former we would now equate with most non-communicable disease epidemiology and the 'epidemiologic method': seeking to deduce 'laws' of nature from the observed facts. In constructive epidemiology Ross states that "we assume what we suppose are the laws, and then try to verify them by inquiring whether they explain all the facts"[2]. It is clear that Ross had a sophisticated concept of this, that this amounted to constructing an epidemiological or mathematical model of disease transmission using the best available biological data to decide on what should be included and that the utility of such a model is in planning how best to control the disease under study.

Second was the application of this approach to understanding communicable diseases and other contagious happenings (such as the spread of rumours or innovations). Ross had a clear picture that the processes were not unique to pathogens and epidemics. His mathematical analysis, in spite of his idiosyncratic terminology and the often unorthodox mathematics employed, has provided the basis for most subsequent work. In particular, his work on communicable diseases generally was taken up by Kermack and McKendrick[3] and more recently in the comprehensive series of studies by Anderson and May.

Third was the specifically malaria modelling. Here his concept of the threshold level of mosquitoes has stood the test of time and underlies the whole theory of malaria control by attacking the vector anophelines. Here his work was taken up by Lotka[4] and a few other mathematicians, but was neglected by epidemiologists until re-worked by Macdonald[5,6] and put into a form that has endured up to the present. Only in the last few years have the discoveries of parasite heterogeneity really raised the need for a revision. This all refers to analytical models, but the computer-based models of Dietz and his colleagues also derive from Ross. What is striking here is the imaginative early work of Ross that has lasted for almost a century and still inspires good work.

Public Health, Sanitation, and the Prevention of Malaria

It only requires a brief perusal of the section on malaria prevention in Manson's *Tropical Diseases* of 1898 as compared with Ross's *Prevention of Malaria*[7] to realise the extraordinary advances achieved in twelve years. Apart from the increase from 5 $^1/_2$ to 700 pages and the fact that, with the demonstration of the mosquito part of the cycle, much that is vague and tentative in Manson becomes clearly seen and clearly stated in Ross, there is a change of atmosphere between the two books. Ross is both modern in approach and highly applied. His goal is stated at the outset: to focus all relevant scientific knowledge upon how to prevent malaria. To that end he sets the subject in its historical perspective, reviews the facts about malaria first in summary and then in systematic fashion. He then develops a theory of the epidemiology of malaria, moves on to discuss each of the possible preventive measures and their implementation. That section again proceeds from general principles through selection of priority approaches to the practical aspects of implementation. The second half of the book consists of contributions from workers in twenty specific malarious countries or situations on what has been achieved in each and by what methods. In layout and content it is a model of how to write a public health text. Both in what it covers and what it omits there is a complete command of the subject. It is better structured not only than its predecessors (which is but to be expected) but also than its successors. Although it is now 87 years old it still repays careful scrutiny. Ross is great stylist as well as scientist, and though his personality is clearly stamped on most of the earlier pages, the paranoiac strain over issues of priority is not as intrusive as in his later writings except in the first chapter.

The second, summary chapter is deliberately written in a simple style and is intended both for the newcomer to the subject and 'for public instruction'. The following chapter lists the key basic scientific results, with evidence, needed for prevention and also reviews (with a completeness that would gladden the heart of a modern review editor) all recorded transmissions of malaria between people either by direct inoculation or through mosquitoes. Ross goes on to discuss pathogenesis but again in very different terms from Manson who is preoccupied (rightly) by detailed qualitative descriptions. Ross is concerned with numbers: how many parasites enter the mosquito or the person bitten, what are the numerical consequences of logarithmic proliferation, how many merozoites per schizont and how many parasites to first cause a fever. He describes the thick smear method that he was instrumental in developing. He cannot resist tabulating the first five powers of numbers from 5 to 20, to help in working out the consequences of different numbers of merozoites per schizont. Ross goes on to look at community aspects of pathogenesis and infection, recording relations to spleen rate to altitude, seasonality of clinical disease and the duration of untreated infections. He also gives rigorous definitions of the various indices of malaria in the community and distinguishes clearly between indigenous cases and imported cases.

In his examination of the mosquito phase of infection, Ross maps the relation of breeding places to the spleen rates in nearby inhabitants, and introduces the measurement of mosquito density as a ratio to the human population. He uses emergence traps to assess output of new mosquitoes and discusses the survival of mosquitoes (here hypothesis and frank speculation take over in the absence of data).

Ross assesses the mortality due to malaria, and seeks to measure economic loss from the disease. He is quite cautious about what appear to be extreme values and shows an understanding of marginal as well as overall costs. His discussion of prevention starts from his epidemiological model, and this is used to show the potential of each possible preventive measure, so that the practical matters of prevention are set in a theoretical framework– unusual in public health both at that time and subsequently. However, once specifics are addressed he is eminently practical and his account of how to use bed nets would be hard to improve upon today.

The discussion of how to select methods for public prevention is admirable. It points out that any method, fully applied, can potentially eradicate malaria (and his implicit definition of eradication is the current one), that the threshold level of some is enough, and that two methods applied partially may be as good as or better than one applied more completely. He discusses the economics of selecting the best approach, with a clear understanding of private and public finance. He suggests the cost of protection against bites by bed nets and screening may be too expensive: "Although it possesses what some governments may consider to be an advantage, namely, that it does not make direct demands upon their own finances, it may yet be in the end more costly to the public than other measures". Similar comments are made by some of us today! In the last section, implementation is discussed in great practical detail, exemplifying Ross's earlier statement that "we should be more scientific in our habits of thought and more practical in our habits of government".

This section of the paper has grown, as the more one reads of Ross's book[7], the more impressive, balanced, and up-to-date it appears. Here is Ross's many-sided genius expressed most constructively and in a balanced way. May be it should influence us more today.

Ross, perhaps more than any other worker in and writer about public health, was able to harness basic science, combine it with quantitative analysis at individual and community level, and bring it to bear on practical problems of improving health. This view was continued in the Ross Institute, particularly through George Macdonald, and subsequently is the main approach of the London School of Hygiene and Tropical Medicine, and of many other development institutions orientated towards tropical health. We should not underestimate the importance of Ross in the movement.

Dichotomies in Malaria: Public Health and Medical Care

Ronald Ross had a clear picture of the role of public health or, as he would have termed it, sanitation. This went far beyond malaria, and in his book are set out ten broad principles which show his relatively rigorous approach[7]. Indeed the World Bank report[8] on health would subscribe to many of them. They are top-down principles however, seeking methods that require minimum input from people as private individuals and maximal effort from governments. He was perhaps the most lucid exponent of the public health as distinct from medical care approach to disease problems in the tropics. Manson conveniently represents the opposite approach of the clinician. To that extent Ross may be seen as maintaining the public health approach : a view which particularly needs support at the present time both in India, UK and elsewhere.

But in relation to malaria, Ross was in part responsible for a sequence of dichotomies in the control of malaria. The issue focussed on India, where the ill-conceived Mian Mir experiment in malaria control by means of preventing anopheline breeding was the source of violent disagreements. The experiment did not work. It proved nothing either way, as the terrain was unsuitable, the study population inappropriate, and the work begun before enough mosquito ecology was known to enable to sound plan to be made. Ross, with his paranoiac dislike of the Indian authorities, saw in this a deliberate attempt to wreck his work. Unfortunately, the first person in charge of Mian Mir was S.P. James, at least as opinionated and intransigent as Ross and who became immensely influential in the Malaria Committee of the League of Nations

Health Organization which consequently belittled the role of mosquito control throughout the 1930s. The sequence of events is discussed fully elsewhere by the author but one aspect was the way in which malaria control split between mosquito control on the one side and multiple approaches of a more general type on the other. There can be little doubt that personality conflicts helped create this sharp dichotomy – the feuding between James and Ross went on even beyond Ross's death, when Watson took over Ross's side of the argument – but the consequences carried over into the controversies about global malaria eradication during the DDT era, where Ross's successor after Watson, Macdonald, was a major protagonist for the global programme. Ross was firmly on the side of those who believed that disease control is a primary goal and that it will alleviate poverty as well as misery.

We, therefore, see that Ross, by his towering and wide-ranging intellect and rigour of thought, as by his meticulous and determined parasitological work, has left a range of intellectual legacies that have carried through even to our generation. His ideas can often guide and always inspire us even today.

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Contemporary Scenario of Medical Research (One Hundred Years Ago)—With Special Reference to the Work of Sir Ronald Ross

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INTRODUCTION

Years after a discovery which had bedeviled the best contemporary scientists it is difficult to envisage the prevailing environment at the time of such a discovery. Global meet organized to celebrate the centenary of the discovery of the role of mosquitoes in the transmission of malaria, provides us an opportunity to briefly survey the medical research scenario in the country at that time. The later half of the 19th century was bristling with activity attempting to discover the causative organism responsible for a variety of infectious diseases. Dominated by the researches of Pasteur, Koch, Lister and their colleagues and contemporaries the causative organisms for tuberculosis, cholera, plague, anthrax, diphtheria, erysipelas, puerperal infection had been discovered. Similarly, parasite for filaria and its mode of transmission was established. It was only in 1880 that Laveran discovered the malarial parasite. Though the role of mosquitoes in its transmission was suspected by a host of researchers, Laveran, Bignami, Manson and others, it was left to Ross to establish the exact mode of transmission. The following account attempts to capture the environment in which this discovery was made.

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The year 1897

" The present has been a very eventful year in India. A serious outbreak of plague in Western India, a severe and extensive famine (in India) in Central and Northwest India, and an earthquake of unusual gravity and area in Bengal and Assam, constitute a series of physical disasters..." stated an Editorial in the *British Medical Journal* (BMJ)[1].

The year was also eventful in several other respects. This was the year when Queen Victoria was celebrating the Diamond Jubilee of her reign. The British empire was fully entrenched in India, four decades having already elapsed since the "First War of Independence" (as we call it) or the Mutiny (as the British described it) had been decisively won by the latter. British were occupied in establishing a 'civil society' based on their own beliefs, perceptions and interests. As a strategy it was important to appear "just", "sensitive to local needs", attempting to improve "local environment and sanitation" to prevent the prevalent scourges of infectious diseases which were responsible for millions of deaths (four million from malarious fever alone) not only of the 'natives' but also the rulers and their loyal armies. These efforts though meant to "succour the indigent and starving and to avert death... calculated to allay anxiety and give rise to a sense of gratitude and good will..." often ruffled the sensitive "native sanctities"[1].

The memories and lessons derived from the first ever Medical Congress held in India at Calcutta from 24-29 December, 1894, were still fresh in the mind of medical personnel in India, but ripples had also reached the policy makers in England (more of this later).

The January 2, 1897 issue of BMJ informs us that the Government of Bombay, probably prompted by the devastating epidemic of plague, "recognized the importance of knowing more of the nature of the disease by appointing a scientific committee, including Professors Haffkine and Hankin to investigate the matter". " The Anglo-Indian public have recognized the need for bacteriological research in support they have given to the scheme for a Pasteur Institute. The Government had promised to encourage the scheme by every means"[2].

It was in the eventful year 1897, Joseph John Thompson identified what is now called the electron, his student Ernest Rutherford distinguished between alpha and beta rays, Marie Curie identified the uranium atom as the source of "Uranium rays". In the field of medical sciences Emile van Ermengem found the bacillus of botulism, Masanori Ogala implicated rat fleas in the cycle of bubonic plague epidemics. And of course Ronald Ross on 20 August observed in the stomach walls of *Anopheles* mosquitoes black granules that pointed towards their role in transmission of malaria[3].

Sir Joseph Lister was the first ever a medical man to enter the House of Peers[4]. Dr. Patrick Manson was appointed Physician and Medical Advisor to the Colonial Office[5]. It was no mere coincidence that these two dignitaries were instrumental in setting up a Royal Commission to investigate thoroughly the question of malaria and allied tropical diseases[6]. In November 1897, Surgeon Major A.M. Davis was attached to the Office of the Principal Medical Officer in India for carrying out bacteriological and sanitary investigations[7]. We also learn that it was in 1897, that Ross, who has been "employing three months leave in investigating the malaria-mosquito theory in Ootacamund" himself contracted the infectious disease. It is a reflection of Ross's importance that BMJ adds, "we trust that the devotion which he has shown in the cause of medical science and humanity will have a better reward than a dose of jungle fever, and that every facility will be granted to enable to bring his disinterested and arduous labours to a satisfactory conclusion..."[5]. Earlier the same year, an annotation on a paper by Ross, "A condition necessary for transformation of Malarial Crescent", the Journal commented, "Malaria is, perhaps, the most important disease affecting mankind". It reminded the Government of "A neglected responsibility of Empire", pointing out that, "In England too little attention has been paid to many pathological and biological problems offered by malaria"[8]. The only significant name amongst the British medical scientists involved in malaria research is no doubt that of Patrick Manson, whose paper on "Method of staining the malaria flagellated organism" appeared in BMJ[9], and his book on Tropical Diseases the next year. It is obvious that Manson and Ross had close interaction.

It may be pointed out that notwithstanding wide spread skepticism, not only in India but all over the world, the microbial origin of infectious diseases was receiving increasing acceptance. Robert Koch had already visited India nearly a decade earlier. The meticulous and extensive work of Haffkine, a pupil of Pasteur, carried out against all odds in the Punjab, Assam, Calcutta, Agra, Aligarh, Gaya, Cawnpore (now Kanpur), Lucknow, involving more than 32,000 victims of cholera, including the trial of his vaccine was widely acclaimed at the 1894 Congress. The malarial parasite was already discovered in 1880 by Charles Louis Alphonse Laveran, a French army physician working in Algeria. It is interesting to note that the word malaria was derived from "mal" "air" or bad air. Laveran's work, even though published in the Journal of the French Academy of Sciences, was looked at with skepticism by leading malariologist of the time like Marchifava and others of Italy. Even Ronald Ross did not accept this till 1894, when he was shown this by Patrick Manson, during his home leave in London. It is claimed that Heinrich Mackel had described similar findings as early as

1847, which was later confirmed by-Virchow. At the 1894 Congress, Surgeon-Lieutenant-Colonel A. Crombie demonstrated the Laveran's body and confirmed its universal presence in the blood of malaria patients in India. Ross was at this time away to London on home leave, but Mr. Ernest Hart the Editor of BMJ, one of the most honoured guests of the Congress, in his address attributed the transmission of disease to drinking water, and therefore, "eminently preventable"[10] (more of this later on). While Hart's contributions to 1894 Congress portrayed him as a genuine friend of Indian medical fraternity, the reviewer of Patrick Manson's book "Tropical Medicine" published in 1898, commented that, "The late Editor of the British Medical Journal used to act, write and speak as if he doubted whether any good useful scientific work could emanate from the Indian Medical Service, yet we find Dr. Manson citing some of its members in nearly every chapter"[11].

The First Indian Medical Congress

A glimpse of contemporary medical research : It will be of interest to look at the overall scenario of medical research in the last years of the 19th century. The proceedings of the first Medical Congress, held at Calcutta between 24-29 December, reported in great details in BMJ by no less a person than Mr. Ernest Hart, the Editor, who personally attended the Congress, provided a glimpse of the prevailing environment. Nearly 800 medical men, from all parts of the country, from Kashmir to Kanya Kumari, belonging to both civil and military services as well as private practitioners, attended the Congress[12]. It may be pointed out that a report in Guy's Hospital Gazette for August 1897, informs us that there were 648 officers in the Indian Medical Service. While all seem to have military designations "309 were in military and 339 in civil employ"[13]. There were also some foreign participants. The Congress was inaugurated by the Viceroy Lord Elgin. The President of the Congress Surgeon-Colonel Harvey referred to the progress which had been made in medical knowledge and teaching since he joined service in Bengal 30 years earlier. He reported a decline in the death rate among British troops in India from 69 to 15 per mile.

Not surprisingly a significant part of the Congress was devoted to bacteriology. The BMJ correspondent commented, "The papers on bacteriological subjects... made up in quality what they lacked in numbers, and may be said to mark an epoch in the history of Indian bacteriology". Cholera research, along with 'malarious' fevers seemed to dominate the scene. Not only cholera was widely rampant but a report by Dr. A. Mitra, Chief Medical Officer, Kashmir, on two major outbreaks in 1888 and 1892 revealed 70 per cent mortality, i.e. 11,712 out of 16,845 patients who received medical aid died. Prof. Hankin of Agra reported his investigations on the causation of cholera, and the recent outbreak in Kanpur. BMJ correspondent considered these as "excellent examples of skilful research carried out with great labour and under great disability from climate and from insufficient assistance, by accurate scientific methods of investigations to absolutely conclusive results. He has demonstrated beyond doubt the immediate causal connection between cholera bacillus and every outbreak which he has yet investigated". In this connection Haffkine's work on cholera and his vaccine trial came for well deserved acclaim, ... "work which he has been carrying on for two years, continuously devotedly and with self-sacrificing enthusiasm, of which there are indeed few parallels". On his part Haffkine was a paragon of humility and scientific objectivity as is obvious from the conclusion of his talk "that immunity hither to shown by the inoculated might on one hand be due to a series of accidents, but it might also, which was more probable, be due to an actual increased power of resisting the disease"[12,14]. Thus the etiology of cholera was put on firm footing, notwithstanding the persistent opposition to this theory by no less a person than Dr. Cunningham, the Chief Government Scientific Official posted at Calcutta. The prevailing view amongst the "Sages of Calcutta" (then capital of India), was still against the microbes to be responsible for most diseases. In this connection it is worth quoting a sarcastic comment of the correspondent, "Hitherto Indian bacteriologists have been particularly successful in obtaining negative results, and such originality as they have shown has expended itself chiefly in the production of ideas about "blue mists" and "aerial miasm" which were regarded as explanations of the origins of "cholera epidemics". I am sure this comment did not apply to Prof. Hankin whose other commendable presentation at the Congress dealt with "Microbes of Indian Rivers", a study diligently carried out for several years on water from various rivers in the North-west Provinces (present U.P. and Punjab). This included weekly observations for one year on water from Jamuna at Agra. He found far less number of microbes in these rivers compared to the reports from several European rivers. In addition he claimed to have observed bactericidal effect of Jamuna and Ganga water on Cholera vibrio within a few hours but the enteric fever microbe was not disinfected by these waters[15].

Fevers of all kinds including a variety of "malarious" fevers, typhoid, remittent fever (etiology ?) along with, filaria, dysentery, ankylostoma infestation, mycetoma constituted some of the other infectious diseases which attracted the attention of investigators. However, it is obvious that various facets of malaria research, its clinical manifestations, diagnosis, prophylaxis and treatment were matters of great concern. Though still not generally accepted as the cause of malaria, Surgeon-Lieutenant-Colonel A. Crombie, the President of the Section of Medicines and Pathology, demonstrated specimens of the Laveran's bodies (malarial parasite). None of the papers on the subject refer to the role of mosquito in its transmission, which was still attributed to drinking water. The beneficial effects of use of the thermal waters of Carlsbad, or alkaline saline waters or the use of hill climates for prophylaxis, treatment and recuperation from malaria provide interesting reading, but without any supporting scientific data. The splenic enlargement with marked anaemia was better treated by a long sea voyage, (obviously a trip back home !) none of this speaks highly of any scientific culture prevailing at that time.

Surprisingly I could find no reference to small-pox and plague, which devastated western India three year later, nor any investigations on tuberculosis which was responsible for many deaths not only in India but also in UK and Europe.

It is interesting to note that already in January 1897, BMJ, wrote a commentary on a paper by Ross published in *Indian Medical Gazette* of October 1896; " This short but pithy paper is a severe criticism of Surgeon-Lieutenant-Colonel Lawrie's extraordinary views on the nature of Laveran's bodies ... Ross with commendable candor tells how he himself was at one time a skeptic on the subject of malaria parasite, how he became converted, and how he repented. He prophesies similar conversion of his colleagues"[16]

At a meeting of the South Indian Branch of the British Medical Association[17] Ross presented a paper on experimental production of malarial fever by the mosquito. Interestingly, "Four experiments were made with a view to ascertain whether bites of mosquitoes fed on malarial blood could transfer *Plasmodium* and the disease it is associated with to the person bitten. *In every case the results were negative*". On the other hand "water containing the debris of mosquitoes fed on the blood of a patient suffering from aestivo-autumnal malarial fever was administered to ten healthy individuals. In seven there was no result apparent, but in three febrile disturbance ensued. In one instance the fever was smart (103°F); in another two it was of no great severity, in the former it was accompanied by presence of ring form of Plasmodium".

Contemporary Environment for Medical Research

Deliberations of the 1894 Congress once again provide a glimpse of the prevailing facilities and environment for research. One learns about the perennial laments of the inadequate funds and facilities, callous attitude of the officialdom, intolerable working conditions resulting in neglect of scientific pursuit prevalent in any poor country even today. Referring to the address by the Governor-General, "tempered of course, by the caution of a great official whose hands are tied by higher powers at home, conscious of a highly depleted exchequer, and under the pressure of the economical screw which is just now applied with increased pressure and which the medical services are the first to feel". This was responsible for, " The short handed condition of the service, which throws extra work on the officers, overwhelms them with official reports and writings and leaves them little time for study or clinical investigation of their cases in any thorough and scientific manner". This was compounded by "The bareness, the miserable poverty of their clinical equipments; the dearth of hospital and school laboratories for such studies of disease and treatment, the want of microscopes and clinical apparatus, these are all signs of the poverty of this country...". One could easily with minor modification say the same for conditions a hundred year later. The commentator goes on to blame the authorities, "There is no great perception of vital importance of some of the latter direful needs among the majority of the elder heads of the departments, and of course, among the lay chiefs there is absolute indifference and utter ignorance". And he laments, "Of the fact that microscopic examinations of the blood and tissues of the diseased body and chemical clinical study are as essential now as 'feeling the pulse' and 'looking at the tongue' were, in the days when they went to school. Many men of official leading here are still not only ignorant, but incredulous"[10]. In another presentation, the author criticised the prevailing theory that "official seniority was identical with scientific infallibility" as pointed out that "the oldest Surgeon-General was not necessarily a more competent bacteriologist than the youngest Surgeon-Lieutenant". There was an unanimous condemnation of the prevailing concept of " The Twenty Man Power Medical Officer" which the Indian Government from motives of economy, exact from a single Medical Officer-in-charge of a province, a goal, a lunatic asylum "..." etc.

This opinion finds its echo in a letter to the Editor which states that all members of the Indian Medical Service who are qualified to offer an opinion on the subject feel that "scientific ambition is, as a rule treated with official indifference and neglect and that work in medical research, be it ever so valuable, will lead to neither promotion nor honour is widely spread and is only too well founded"[12]. Similar sentiments are expressed in a note "by an officer of experience and seniority". "If the Government of India want diseases studied in a proper manner they should provide proper bacteriological appliances and central laboratories, but as a matter of fact this they have not done. It is nonsense asking men to make bricks without straw. Bacteriological research in India is of vital importance"[17]. As mentioned earlier the only Central Bacteriological Laboratory at that time was at Agra under Prof. Hankin, and the Government of India had plans to establish "Pasteur Institute" at Kasauli or Pondicherry and at least another laboratory at Calcutta. The man who had worked hard for these development Mr. Ernest Hart died in early 1898, before the fruition of these dreams[18].

Some Contemporary Views on Malaria and Mosquitoes

Prevailing confusion regarding clinical manifestations of malaria: An editorial: "That comfortable word Malaria" published in March 1898, highlighted the prevailing confusion in respect to the diagnosis of malaria. "Undoubted tendency to ascribe many diseases and symptoms to malaria on no surer grounds than that the patient has at one time suffered from malaria or has resided in a country in which malarial fevers are known to be endemic". Mention is made of chronic atrophic cirrhosis of liver, some forms of haematuria, malarial orchitis, hydrocoel, neuralgia, cerebral paralysis etc. Editorial clarifies that many of these are secondary diseases affecting anaemic, debilitated persons.

Another editorial: "The abuse of the term Malaria" commenting on a paper by Dr. Rupert Norton published in the *American Journal of Medical Sciences* in February 1898, points out that "malaria has not yet been recognized as a disease with as definite a set of symptoms as typhoid or any other of the infectious diseases". Norton gives a list of diseases which various writers have without real foundation attributed to malaria, e.g. disease of nose, eyes, ears, heart, lungs, intestine, spleen, kidneys, central and peripheral nervous system. De Mello from Brazil experience, gives a list of thirty-one "malarial diseases" from erythema to metroperitonitis[19].

Malaria and mosquito: It appears that Manson's Goulstonian lecture in 1896, where he proposed mosquito as the alternative host of the malarial parasite started a major discussion on transmission of malaria. Bignami from Italy wrote a lengthy critique of this presentation in *Policlinic* July 10, 1896. Manson believed that the so called flagella are in reality flagellate spores intended for the continuance of the life of the parasite in some suctorial animal. Bignami on the other hand was convinced that even the patients crescents seen in blood of malaria are "deviate and sterile forms" and that the flagellate bodies are products of degeneration. However, Bignami advanced his own theory of role of mosquitoes in malaria on certain epidemiological considerations. Refusing to admit either water or air as the medium of malarial infection, he concluded that infection must be produced by inoculation by mosquito. In support of the degeneration theory Bignami quoted the work of several of his contemporaries like Antoliser, Grassi, Feletti and Bastianelli.

Ross who had an opportunity to personally discuss with Manson his views, summarised the two opposing views of the latter and Bignami as follows: "Fortunately the theory as developed by Manson is founded on something far more solid than such merely plausible conjectures as Bignami has to advance. It is founded on his induction (for which we are indebted to him and no one else) that the process of exflagellation is a developmental one included by nature to continue the life of the species within some suctorial animal. The epidemiological considerations serve only to fortify the presumption that the suctorial animal is the mosquito". It was this, controversy which Ross discusses at great length in his paper "Observation on a condition necessary to the transformation of the malaria crescent"[20] wherein he provides experimental proof in support of Manson's evolutionary hypothesis. In this paper Ross remarks, "It is interesting to note that Bignami has not succeeded hitherto in finding the parasite in mosquitoes — an experience which so far as it relates to the post-flagella stages, coincides with mine upto the present. His argument, delivered with much confidence, that it is impossible for the mosquito to convey the parasite out of human blood...".

Undettered by Bignami's theoretical objections and finding support in Ross's experimental work, Manson described a "Method of staining the malarial flagellated organism"[9]. In December 18, 1897, issue of BMJ, Ross reported, "On some peculiar pigmented cells found in two mosquitoes fed on malarial blood"[21]. In its introduction Ross points out, "For the last two years I have been endeavoring to cultivate the parasite of malaria in the mosquito. The method adopted has been to feed mosquito bred in bottles from the larva, on patients having crescents in the blood, and then to examine their tissues for parasites similar to haemamoeba in man. The study is a difficult one, as there is no *a priori* indication of what the derived parasite will be like precisely, nor in what particular species of insect the experiment will be successful...".

Ross sent his slides to Surgeon-Major Smith, who in turn got these examined by Dr. Thin, Mr. Bland Sutton and Dr. Patrick Manson. Manson sent a detailed report, I quote here only one sentence, "I am inclined to think that Ross may have found the extracorporeal phase of malaria. If this be the case, then he has made a discovery of the first importance". Future events confirmed Manson's prophesy.

Ross quickly followed this with another paper, "Further observations on the transformation of crescents"[22]. In concluding this paper, Ross asserted, "That the fact that transformation will not occur at all unless the density of the blood is changed deals a final blow to the theory of Autoliser, Bignami, Bastianelli and others that exflagellation is a process of degeneration due to death. The process, therefore, cannot be one of death, it must be one of life, and being such, must have some significance in life history of the parasite... that transformation is meant to occur in the stomach of the mosquito...".

Ross in search of epidemiological confirmation of the mosquito hypothesis took leave to study the problem in Ootacamund. This is the subject of his paper in *Indian Medical Gazette* : April, 1898. "Report on a preliminary investigation into malaria in the Sigur Ghat, Ootacamund..."[23]. This paper reveals the lingering doubts in the mind of Ross regarding the "mosquito theory" of transmission of malaria as revealed by the following: "And it now became obvious that in that locality at least, malarial infection may be produced either by contact of the insect with the human skin as insisted upon by Bignami or by people drinking water out of jungle pools when thirsty or perhaps by both means"... "The water theory is also possible". "I feel inclined to admit as a result of my brief investigations that mosquitoes are plentiful enough in the Sigur Ghat to account on the supposition of the mosquito being the alternative host of the parasite, for the presence of malaria in that locality. At the same time I must carefully guard myself from being held to mean that I have found more epidemiological evidence for the mosquito-hypothesis than for the other hypothesis already defined"... "that the hypothesis of the X-protozoan living free in the air, water, soil, is just as probable, if not more so, than the mosquito theory"[23]. It is obvious that Ross was unwilling to challenge the latter hypothesis which had the backing of Manson. By this time Laveran's *Traite du Paladisme* (Paris 1898) had been published. Writing under *Current Medical Literature* malaria in the Mauritius W.J. Buchanan in March 1898, issue of *Indian Medical Gazette* quotes from M. Laveran's *Traite du Paladisme* about the endemic malaria in Mauritius occurring only after emigration from India in 1869 (malaria was unknown there in 1867).

The author also quoted Laveran (page 123 of his book) "While admitting the numerous cases he quotes of malaria being conveyed by means of drinking water are not beyond dispute, gives a list of arguments in favour of the theory started by him which has been so developed by Manson and Surgeon-Major Ronald Ross". Furthermore, Laveran writes, "The constant failure to culture the haematozoan in water or soil seems to prove that this organism is found in a different form in external media to that seen in the blood, and that it has probably an intermediate host". Laveran was led to suspect mosquito on account of what was known of the propagation of filarial disease by that insect. He provided nine points in favour of involvement of mosquitoes. It is interesting to note that Laveran does not maintain that the mosquito directly inoculate malaria, "But that the organism sucked out from malarial blood by the insect passes a phase of its evolution in the mosquito, and then finds its way into drinking water and thence into the human system". Laveran then proceeds to detail the valuable observations in support of this theory by Manson and especially by Ronald Ross.

Manson in July 1897, issue of the BMJ commented on the recent observations of Ross on certain cell forms in the stomach of mosquito. He informs us that Koch and Laveran appear to have accepted the mosquito theory, and on the whole its position at the present moment seems to be some what firmer than it was sometime ago. "Much still remains to be done to establish it on a satisfactory basis".

It is remarkable that the reviewer of Manson's book on the Tropical Diseases, published in early 1898, had such uncharitable comments to make about his write up on malaria, "The whole argument spread over half a dozen chapters is a piece of special pleading in favour of the *Plasmodium malariae* as the cause of malarial disease and in favour of the mosquito as *particeps criminis*". "... when it comes to malaria he throws caution to the wind (which is the hallmark in discussing aetiology of cholera or dysentery) and goes neck or nothing for his pet hobby". The reviewer goes on, "Let us hope that Plasmodium gospel and the mosquito theory will eventually prove correct, and it will be an immense stride towards the elucidation of present chaotic want of knowledge of Indian fevers. But we hold that Manson and the whole BMJ School have yet to prove that the Plasmodium is the cause and not an effect of malarial fevers and also that there are no other possible causes which may produce the blood changes"[11].

Robert Koch and Malaria

It is interesting to note that around the same time Robert Koch was first deputed by the Government of Germany to southeast Africa in 1896 for two years to investigate tropical diseases there and then sent to Italy for one year for study of malaria. His lecture on the subject given to a lay audience in Berlin and published in *Lancet*, July 2, 1898 was commented upon in *Indian Medical Gazette*[24]. The commentator probably in deference to the exalted status of Koch, finds some obvious flaws in his assertions without daring to criticise him. Koch is said to have dogmatically stated that there are "Two clinical forms of malaria, one occurring in Europe as quotidian or tertian; the second or malignant only in hot climates which shows very irregular fever". The commentator questions, "Does he understand that quotidians do not occur in tropics? "Is he correct in saying that the relation of the parasites to the different kinds of fever has not yet been ascertained". One of the biggest mistakes in Koch's observations was that, "Blackwater fever (Haemoglobinuric fever) is not malarial, but due to a toxic effect produced by quinine". This view earlier expressed by Murri of Greece (1895) and Tomaselli of Sicily (1888) was strongly challenged by Indian experts in tropical medicine. To refute this contention Captain F.P. Maynard (1898) published a report of a case of malaria with haemoglobinuria who had received only five grains of quinine throughout his illness. In *Indian Medical Gazette*, December 1898, there is a detailed reference to the work of one Mr. Crosse, Principle Medical Officer of the Royal Niger Company, who had recently published a book entitled, "Note on the Malarial fevers met with on the River Niger (West Africa). He selected haemoglobinuric or black water fever, as a special subject of his discourse. He gave strong reasons for discrediting Koch's assertion, "This hasty generalization" which he believed had done great harm by raising a distrust of the efficacy of quinine in the treatment of malarious fevers. Koch had his own theory regarding mosquitoes and malaria. He believed that the mosquitoes probably deposit their eggs on human body and that the parasites issue from these eggs. This presentation of Koch came for further criticism in an Editorial in the October issue of *Indian Medical Gazette*[24].

Notwithstanding the general criticism of Koch's pronouncement, when finally a commission of experts to study malaria and plague was constituted by the Royal Society and the Colonial Office of *Indian Medical Gazette*: November 1898 laments that if, "Germany can depute one of her most distinguished scientists for three years to study tropical diseases such a generous example might well have been followed in the appointment of our Malaria Commission. Its present constitution is a distinct slur on the members of the medical services and the other medical men practising in the tropic". Interestingly, Ross was not a member of the Commission. In contrast the new Plague Commission consisted of two members of the Indian Medical Services besides three eminent medical scientists from England.

Needless to say Ross continued to contribute to this field by publishing a series of papers like, "On some peculiar pigmented cells found in two mosquitoes fed on malarial blood"[21]. "Further observations on the transformations of crescents"[22], "Report on a preliminary investigation into malaria in the Sigur Ghat, Ootacamund"[23], and "Report on the cultivation of proteosoma Labbe in grey mosquitoes"[25].

CONCLUSIONS

In conclusion, it is obvious to the author that the scientific researches of Ross were carried out under the most difficult circumstances, with minimal support, in an environment not generally conducive to such work, there being hardly any genuine scientific investigations, other than some clinical and epidemiological studies worth the name being conducted in the country at that time. His colleagues both in India and abroad were, however, very appreciative of his work and I could find no criticism in any of the large number of publications on the subject. The author does accept his limitations in not being able to probe in greater depth the prevailing scenario, being forced to draw his conclusion on the basis of only a few journals (BMJ, 1894; 1895; 1897 and IMG, 1898) which were kindly loaned to him by the National Medical Library, New Delhi.

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Control of Malaria in the World

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Historical Account of Malaria Control

The final confirmation of the mode of transmission of the malaria parasite by the mosquito vector by Ronald Ross in Secunderabad in 1897 provided the hope that the disease which had been the scourge to civilization since prehistoric man could be controlled or even eradicated. In spite of a century of research and control efforts, malaria is still a major global health problem and an obstacle to social and economic development.

World Health Organization (WHO), from the time of its inception in 1948 and before that through the Interim Commission of the WHO, has given highest priority to the global problem of malaria. Estimates of disease incidence made at the end of the 1940s indicated that, globally each year, malaria was responsible for the death of some three million people and directly affected the health of more than 300 million[1]. This was more than any other tropical disease incidence. Malaria epidemics were also common, occurring mainly in Africa, Asia, particularly South and Southeast Asia, and Central and South America.

About 10 years earlier, Sinton (1935) had estimated that malaria in India directly caused the deaths of at least one million persons and was indirectly responsible for atleast two million deaths each year. This represented a case fatality rate of 1% in an estimated 100-200 million clinical cases[2]. These estimations related to colonial India,

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which included at that time and other countries in South and Southeast Asia.

In response to this alarming situation, the WHO in 1955 launched a Global Malaria Eradication Programme aimed at the elimination of the malaria parasite in the majority of endemic countries. This was based on widespread intradomiciliary spraying with DDT and treatment of infections with antimalarial drugs, mainly chloroquine. This international effort to eradicate malaria did not include most of Africa, South of the Sahara (with the exception of Ethiopia, South Africa and Zimbabwe). Vector control interventions were not considered feasible in most of this region because of high intensity of malaria transmission and the limited health infrastructure available to support such a programme.

As a result of the Global Malaria Eradication Programme, malaria was eradicated by 1967 from all developed endemic countries, and large areas in tropical and subtropical Asia and Latin America. Between 1955 and 1967, the population freed from the risk of disease had increased from 220 to 953 million and direct mortality from malaria decreased to less than one million, most of which were in tropical Africa[3]. In India alone, morbidity and mortality was reduced to about 100,000 clinical cases and one thousand deaths each year.

In spite of the achievements of the Global Malaria Eradication Campaign, there was a realization that the objectives of global eradication of the disease and maintenance of a malaria-free status could not be achieved without the existence of a well-developed and public health-oriented infrastructure. It also became obvious that the improvement in the malaria situation achieved could not be maintained indefinitely without a substantial increase in national commitments and in international assistance in view of the mounting operational, financial and technical problems faced by the programmes. In retrospect, it is easy to see a solution was sought by over-simplication and standardization and that many of the programmes lacked epidemiological and administrative expertise. These factors were overlooked because of the humanitarian appeal and urgency. In addition, technical restraints such as vector resistance to DDT and of the parasite to chloroquine began to affect programme activities.

The recognition of these constraints led to the re-examination of the malaria eradication strategy by the World Health Assembly in 1969[4]. An almost immediate reaction was a considerable reduction in the financial support to antimalaria programmes, both from international and bilateral sources, except WHO, and it continued to provide countries with technical and financial support.

The capabilities of malaria endemic countries to continue the antimalaria operations were further reduced by the economic and financial crisis which affected the world at the beginning of the

1970s. This resulted in a dramatic rise in the prices of insecticides, drugs and shipping. The need to procure more expensive insecticides and drugs to overcome the mounting problems of vector resistance to organochlorines and *P. falciparum* to chloroquine, further compounded the difficulties.

As a result of the reduction in antimalaria activities, especially those related to vector control, and the inability of the countries to formulate and implement realistic and epidemiologically sound plans for combating the disease, malaria started a gradual and, in some instances, even dramatic comeback in Asia and Latin America. The extensive resurgence of malaria in countries in South Asia and South America, particularly India and Brazil, during the mid-1970s led to a resurgence of interest in malaria, and the recognition of the need to develop national antimalaria programmes keeping in view the local epidemiological situation and national financial and human capabilities. To provide the national programmes with the new malaria control tools, WHO in collaboration with the World Bank and United Nations Development Programme created the Special Programme of Tropical Disease Research in 1975[5] and established the Malaria Action Programme in 1979 to facilitate the implementation of malaria control activities in the affected countries[6].

The pessimism prevailing in some quarters during 1970s, as a result of the devastating consequences of the malaria resurgence, dissolved into guarded optimism. This was the result of the Alma Ata Conference[7] and the hope that a well informed and actively participating community, together with the health services based on the principles of Primary Health Care (PHC), would ensure the necessary infrastructure for the delivery of antimalaria action and the maintenance of the gains achieved. In the wake of these developments, a limited number of African nations such as Ethiopia, Nigeria, South Africa, Swaziland and Zimbabwe developed and approved national antimalaria policies and organized functioning malaria control programmes. The implementation of the malaria control based on the PHC approach was, however, slow. This was due in part to the problems of its interpretation, a reluctance on the part of the governments to move away from the practices inherited from the malaria eradication era, and to delays in the further development and implementation of national health services based upon the PHC approach.

As a result of the measures carried out at the end of the 1970s, the malaria situation outside Africa returned to conditions similar to those prevailing just before the resurgence. During this period, a consistent improvement in the malaria situation has been observed only in China and some countries in northern Africa. In most of the countries of Asia and Latin America, it remained either stagnant or was deteriorating.

Most of tropical Africa continued to face an increasingly serious public health crisis caused by malaria. There has been a large increase in the number of agricultural and industrial development projects and urban settlements associated with extensive population movement from non-endemic to highly malarious areas, increasing malaria risk and high mortality and morbidity. Numerous civil wars and social unrest in various African countries, combined with fluctuating meteorological and ecological changes favourable for the enhancements of malaria transmission in areas previously free of malaria, has also contributed heavily to the increased malaria problem in Africa in the 1990s. Limited national financial resources, the absence of external support, inadequacies in technical guidance and insufficient experience in controlling malaria in highly-endemic areas, has further compounded the problem. The situation has been aggravated by the emergence and spread of chloroquine-resistant *P. falciparum*.

Although the burden of malaria is mainly confined to Africa (South of the Sahara), multi-drug resistant falciparum malaria, that had developed in frontier areas of development in South-east Asia and South America during the 1980s, is threatening malaria control in other parts of the world. This has highlighted the desperate need for new antimalarial drugs and for operational research to understand and contain the problem.

In view of this serious situation, WHO's Executive Board proposed in 1990 that a Ministerial Conference on Malaria should be held to mobilize affected countries and the international community to intensify disease control efforts. In preparation for the Conference, a number of international consultations took place, involving hundreds of managers, scientists, administrators, representatives of donor agencies, research institutions and the United Nations and its specialized agencies. The main objective of these meetings was to reach a consensus on current standards for malaria control and to formulate a Global Malaria Control Strategy, which was then presented and endorsed by the Ministerial Conference in 1992 held in Amsterdam[8].

The Economic and Social Council of the United Nations (ECOSOC) also initiated a review of malaria in 1993, responding to the concern expressed by members of the Council, especially those from countries in Africa, that malaria was not receiving the urgent attention and funding needed from individual countries and from the United Nations system.

ECOSOC's review led to the endorsement of the Global Malaria Control Strategy in the 49th Session of the United Nations General Assembly in December 1994[9]. ECOSOC requested WHO to continue to act as the lead organization for malaria control and to develop an Action Plan (1995-2000) in consultation with other UN agencies, other partners in malaria control and the countries concerned. ECOSOC endorsed the Action Plan in 1995 and called for increasing resources for the prevention and control of malaria[10]

The Global Malaria Control Strategy

The objectives of the Global Strategy are to prevent mortality and to reduce morbidity and social and economic loss due to the disease through the progressive improvement and strengthening of local and national capabilities for malaria control.

It has four basic technical elements: (i) to provide early diagnosis and prompt treatment; (ii) to plan and implement selective and sustainable preventive measures including vector control; (iii) to detect early, contain or prevent epidemics; and (iv) to strengthen local capacities in basic and applied research to permit and promote the regular assessment of a country's malaria situation, in particular, the ecological, social and economic determinants of the disease.

The strategy calls for the rational use of existing and future tools to control malaria. It recognizes that malaria related problems vary enormously from epidemiological, ecological, social and operational viewpoints, and that sustainable, cost-effective control must therefore be based on local analysis. The strategy is firmly rooted in the Primary Health Care approach and calls for the strengthening of local and national capabilities for disease control, community partcipation and decentralization of decision-making for the integration of malaria control activities with related disease programmes, and for the involvement of other sectors, especially those concerned with education, agriculture, social development and the environment. It emphasizes the vital importance of continuing research both locally and internationally, and of international teamwork in research and control.

The strategy differs significantly from past approaches to the malaria problem, especially those used in the eradication era. Its implementation depends on a change in emphasis from highly prescriptive, centralized control programmes to flexible, cost-effective and sustainable programmes adapted to local conditions and responding to local needs. Thus, the strategy aims to control malaria through a concerted approach, using various methods of intervention based on the knowledge of local epidemiology of the disease, available resources and the ability to maintain a sustainable impact.

Action Plan for Malaria Control (1995-2000)

The Action Plan for Malaria Control provides objectives, targets and a timetable of activities for the implementation of the Global Strategy for the period 1995-2000. Priority is given to country support, based on the development of realistic and affordable national plans of action after an assessment of needs and priorities. Training and operational research should be the part of these national plans. The Action

Plan emphasizes the integration of malaria control activities into other health delivery programmes and general health services, especially by strengthening the community's role in prevention and control. Emphasis is placed on better partnership among UN organizations and other agencies involved in malaria control. The Action Plan translates research and technical developments into policy and guidelines, on which training and education materials are based.

Priority is given to malaria endemic countries in Africa (South of the Sahara), where over 90% of the world's malaria cases occur. These countries have an urgent need for the establishment of national malaria control programmes and for the implementation of the strategy at central and district levels. The focus in these countries is on strengthening the provision of early diagnosis and prompt treatment both at the health services' facilities and at the community level, the management of severe and complicated cases, the detection and management of malaria epidemics and the development of strong community-based programmes for malaria prevention and control.

In other parts of the world, priority has been given to reorient existing malaria control programmes in line with the principles of the Global Strategy. This includes the strengthening of curative services at all levels of the health care system, the promotion of rational drug use, provision of health information, and the selective use of disease prevention methods including vector control.

Within these priorities, two main objectives have been set, (i) that by the year 1997, at least 90% of the countries affected by malaria implement appropriate malaria control programmes; and (ii) that by the year 2000, malaria mortality is reduced by at least 20%, in 75% of affected countries compared to 1995

Implementation Status of Global Strategy

Capacity building

In most countries with endemic malaria, there is a shortage of people having knowledge of its epidemiology and planning and management of control. In many, the peripheral health services are unequal to the task of diagnosis and correct treatment. An important element of the Global Strategy is to build up malaria training capacity as part of the efforts to equip all levels of the health services with the competence to control communicable diseases. Estimations by WHO in 1995 of the global training requirements indicate that more than 800 programme managers, 1,500 specialists, 13,000 assistants, 55,000 workers at the district level and 120,000 community health workers are required to be trained or retrained[11]. WHO has developed a malaria training programme in which priority is given to training of district health officers and teams through the training of trainers within the country.

Priority areas in training programmes are: (i) the development, implementation and evaluation of plans of action for malaria control; (ii) disease management by the development and implementation of antimalarial drug policies, the strengthening of diagnostic and treatment facilities and the improvement of treatment in the community; (iii) selective and sustainable preventive measures including vector control; (iv) early detection, containment and prevention of epidemics and timely reaction to emergency situations; and (v) programme management and surveillance to assist countries with the establishment of managerial and epidemiological information systems in monitoring their activities.

Guidelines on all of these subjects have been developed and form the basis of all training activities[12-21].

Other groups require appropriate training include drugs sellers, private practitioners, and people in other sectors such as education, agriculture and development whose activities relate to malaria and its control. At the community level, education enhances awareness and skills empowering people to be active partners in control.

Implementation in African Region

Priority in Africa has been given to the establishment of effective national malaria control programmes, development of plans of action and capacity building to implement these plans.

Most of the 46 malaria endemic countries in Africa have received financial support for developing their malaria control programmes, either from international organizations, or on a bilateral basis. Some of them have shown increased commitment to malaria control by mobilizing additional national resources, e.g. Botswana, Ethiopia, Namibia and Zimbabwe. This has enabled most of these countries to complete national plans of action for malaria control by the end of 1996. Due to the limited availability of human and financial resources, the majority of these plans are in the initial stages of implementation. However, the completion of action plans has been hampered in many of the African countries due to political instability, civil wars and natural disasters.

With the support of WHO and other agencies, over 150 trainers have been trained in Africa. These are now responsible for country level training of district health officers and their teams in malaria management and control. By the end of 1996, nearly 16,000 persons had been trained in malaria control courses at district and community level, emphasizing case management practices, early diagnosis and prompt treatment. For the first time in Africa, each endemic country has at least one person who has been trained to take responsibility for the planning of the control of malaria and other major tropical diseases. The main problem, however, is a continuous turnover of trained personnel as a consequence of lack of government support and limited career prospects. This endangers the development and maintenance of control programmes.

By 1996, over 9,000 persons had been trained in various aspects of disease management. Priority has been given to the district, community and private sector needs of African countries. Training in the management of severe malaria was given to 1,000 health workers from ten African countries and over 400 laboratory technicians from six countries have been trained in basic microscopy. Participants from 11 countries in eastern and southern Africa were trained in new techniques to determine therapeutic efficacy of antimalarial drugs, which will enable the programmes to interpret the results of monitoring drug resistance better and to decide on the national and implementable antimalarial drug policies[19].

Based on the WHO produced guidelines for the selective use of vector control and for operational implementation of insecticide-treated materials in Africa[16,20], entomologists from 26 African countries were trained. Currently, the use of impregnated bednets on a limited scale has been already started in over 20 African countries.

In view of the increasing incidence of malaria epidemics in Africa, general health service staff of 17 African countries have benefited from training in epidemic preparedness and control in epidemic-prone areas, based on the WHO guidelines developed for malaria control among the refugees and displaced populations[18,21]. The knowledge acquired during the training was instrumental in the prompt control of malaria epidemics among the Rwandan refugees in Tanzania and Zaire in 1994-95 and in Zimbabwe in 1996-97.

Efforts have been made in a few African countries to involve the community in malaria control more actively. An example is in the Tigray region of Ethiopia, where ecological conditions are highly conducive for unstable transmission, causing frequent waves of large-scale epidemics. In this area, a community-based malaria control project is being supported by the Regional Government, WHO and the community through the implementation of environmental management, the use of insecticide-impregnated mosquito nets, and the introduction of a cost-sharing scheme at the village level to contribute to the sustainability of the programme. At the start of the project, a seven-day malaria course, including general health training, was given to the Community Health Workers (CHWs) appointed by the communities themselves. Each CHW was provided with antimalarial drugs, a guidebook for reference, and a practical diagram with age-specific chloroquine regimens for display at each treatment site. Within the project, a total of more than 535,000 clinical malaria cases were treated by CHWs during 1996. The CHWs are also engaged in malaria prevention measures, such as provision of chemoprophylaxis to pregnant women, distribution of mosquito nets and the reduction of mosquito breeding places by applying methods of environmental management. In 1996, more than 34,000 persons were involved in source reduction activities in areas with a population of about five million in 2,200 villages. Villages authorities were assisting CHWs with community mobilization.

As a direct result of the community-based malaria control in the Tigray region, there has been a remarkable reduction of malaria transmission in epidemic-prone areas and the overall mortality in children under age 5 has decreased by 35%[11]

Implementation outside Africa

Malaria control activities outside Africa are aimed at the prevention of malaria mortality, reduction of malaria morbidity, prevention and control of malaria epidemics and maintenance of malaria free status in those areas where malaria eradication was achieved earlier.

The Americas: More than 30% of the total population of the region live in areas under malaria risk, approximately 42 million people living in high-risk areas, 36 million in medium-risk areas, and 171 million in low-risk areas. In common with other regions, the risk of exposure varies with a variety of factors that facilitate contact between humans and vectors, such as development, population movements, social instability, and attitudes and behaviour of communities to malaria. Malaria risk is compounded by the limited access to appropriate diagnosis and treatment at highest risk areas.

Following the reorientation of the national malaria control programmes in the region during 1993-1995, the coverage of epidemiological surveillance activities has increased by 10-15% in areas of high- and medium-risk[22]. This increased surveillance, in combination with increased transmission of *P. falciparum* in Bolivia, Colombia and Peru, resulted in moderate increase in the number of reported malaria cases in the region, i.e. total 1.3 million cases in 1995 compared to 1.1 million cases in 1994. Nearly half of these cases were registered in Brazil and a third from the Andean countries of Bolivia, Colombia, Ecuador, Peru and Venezuela. However, the risk of becoming ill with malaria based on incidence per 1,000 total population is highest in the Guianas, Belize and the Amazon areas of Brazil.

Most countries in the Americas have made major steps in integrating the traditional malaria control programmes into the general health services at the central level. To do so, several of these countries have had to revise their legislation to allow for the integration of services and to promote intersectoral collaboration. Major advances have been made in the integration in Bolivia, Brazil, Colombia, El Salvador, Guatemala, Honduras, Nicaragua, Panama, Peru and, to a lesser extent, in

Venezuela. Although the efficiency of the local health services in the detection of cases of malaria is considerably higher than that of active case detection by specialized services, it still requires strengthening in many countries.

The epidemiological re-definition of areas of malaria risk has resulted in the prioritization of areas and an improvement both of the targeting of diagnostic and treatment facilities to those in the greatest need and of the selective use of vector control measures. A clear shift away from the organochlorine and organophosphorus products to a greater use of the synthetic pyrethroids, which have been shown under local conditions to be safer and more cost-effective, has occurred in several countries of the region. There is still, however, a need for increased intersectoral coordination in order to ensure the sustainability of vector control measures. This is particularly important since, by and large, the control programmes are undergoing a drastic reduction in the budgetary funding. Combined with the major administrative process of decentralization of health services, this poses a serious problem for the implementation of the Global Strategy. Some programmes, however, obtain financial support through external loans, e.g. from the World Bank, and grants from outside the health sector budget[22].

Eastern Mediterranean Region: In the East Mediterranean Region, all the countries have revised their plans of action and are in the process of implementation. This is, however, seriously hampered by political instability and civil unrest in a number of countries. For example, both Afghanistan and Somalia have been unable to carry out organized malaria control activities, except in limited areas with the assistance of NGOs. In general, the number of malaria cases reported officially (between 300,000 to 350,000 cases a year) does not reflect the true magnitude of the problem since the most affected countries by malaria are either under-reporting, or have stopped reporting altogether, e.g. Afghanistan.

Information on the number of deaths is either unavailable or not reliable, despite the fact that many programmes are improving the collection of information on morbidity and mortality. The estimated number of deaths due to malaria in the region is about 50,000 a year, the majority of them occurring in Sudan, Somalia and Yemen.

Malaria transmission has been eliminated in a few countries such as Bahrain, Cyprus, Jordan, Kuwait, Lebanon, Libya, Qatar and Tunisia. In these countries, all efforts are directed towards the improvement and maintenance of an efficient surveillance system, capable of preventing the re-establishment of local malaria transmission from the ever-increasing importation of malaria from endemic countries. The current activities are, however, based on the campaign approach of malaria eradication and, as such, there is a need to review and update them according to the principles of the Global Strategy (A. Beljaev, 1996: Personal communication).

In the other eight countries of the region, i.e. Egypt, Islamic Republic of Iran, Morocco, Oman, Pakistan, Saudi Arabia, Syria and the United Arab Emirates, national control programmes effectively control malaria throughout their territories. In many of them, malaria is focal, transmission continuing only in certain limited areas. Due to intensified antimalaria activities, there is a marked reduction of malaria in Morocco and Oman and eradication seems to be a practical proposition in Morocco as well as in Egypt.

In contrast, there is a tendency for an increase in the number of cases in Pakistan, especially in Sindh and Balouchistan Provinces and the malaria situation has deteriorated in Afghanistan, Djibouti, Iraq, Somalia and Yemen, where population coverage by the malaria control programme is incomplete due to internal security problems. Although massive malaria epidemics did not occur in Djibouti and Sudan in 1995 and 1996, as was the case in 1994, this could have been attributed to a decrease in rainfall rather than to successful antimalarial operations. In Yemen, vector control activities could not be maintained in 1995 and 1996 due to insufficient funds, the situation being further aggravated in 1996 by excessive rains. This resulted in an epidemic outbreak, causing several hundred deaths due to the non-availability of antimalarials at the periphery.

Resumption of vector control activities in Iraq, following large-scale malaria epidemics in 1994 and 1995, has reduced the incidence of malaria in the three northern governorates of the country. Despite the setbacks that afflicted malaria control in Iraq, this country is free from *P. falciparum*.

Technical problems, such as spread of chloroquine-resistant *P. falciparum* and increasing resistance of vectors to insecticides, continue to hamper control activities in many countries of the region. Resistance to chloroquine has been reported from every country where *P. falciparum* is present, with the exception of Fayoum Governate in Egypt. However, the level of resistance is such that chloroquine may be still used as a first-line drug.

Some programmes are chronically dependent on external support for the supply of drugs and other basic materials. Steps are being taken to increase self-sufficiency by promoting both local formulation of the drugs and manufacture of insecticide impregnated materials. Emergency supplies were provided in 1996 by WHO and other agencies to areas affected by malaria epidemics in Iraq, Somalia, Sudan and Yemen.

WHO supports training activities in the region, including fellowships and training courses at country and inter-country levels. A newly-organized Training Centre in Wad Medani, Sudan completed its first nine-month Master Degree Course in 1996 and attempts are also being made to restore International Training Centre activities in Iran.

Insufficient and poor feedback of epidemiological information continues to contribute towards delayed antimalaria responses, particularly in relation to forecasting and contributing malaria epidemics. A retrospective analysis indicates that many malaria epidemics that occurred in the region recently could have been predicted, or at least detected at the earlier stages if a simple monitoring system of malariogenic conditions had been established in epidemic-prone areas.

A small grant's initiative for operational research in tropical diseases has been established in the region. As part of this initiative, WHO has supported in 1996-97, five operational research projects in Egypt, Sudan and Yemen related to malaria stratification, therapeutic efficacy of antimalarial drugs, environmental measures for control, impregnated mosquito nets and epidemiological indicators for epidemic prediction.

Border meetings between neighbouring countries within and outside the region regularly take place for better exchange of information and concerted action for malaria control.

Southeast Asian Region: All the endemic countries in the Southeast Asian Region are implementing plans of action that were revised in 1993-94 and based on the principles of the Global Strategy. In both this Region and that of the Western Pacific, the integration of malaria control with the strategy of primary health care varies in keeping with the way each country has developed its primary health care activities. Integration with the general health services exists in many countries but problems exist at the periphery where workers have difficulties in giving time to the necessary health education and preventive measures of the various programmes under their responsibility.

The main priority in the Southeast Asian Region has been given to improve the effectiveness of the programmes, which had declined during the 1980s and early 1990s, as a result of a poorly managed decentralization and integration of malaria control activities. Through this process, malaria control programmes had lost their essential features of unity of purpose, dedication of staff, commitment of achieving objectives, and flexibility of action under changing epidemiological conditions. Thus, many programmes lacked the technical expertise, both at central level to plan and evaluate a national programme and at intermediate and at peripheral levels to manage and implement it. The programmes were also severely hampered by inadequate funding and lacked information systems that were sufficiently sensitive, reliable and timely to identify emerging epidemics and to sustain a logistical capacity to provide an adequate and timely response.

Thus, seminars and workshops have been conducted for training and refresher training of various categories of general health service staff, malaria staff and community health workers in various aspects of malaria control, including disease management, selective vector control and epidemic forecasting and control. With the support of WHO and other partners in malaria control, 76 persons were trained in WHO-sponsored international courses in programme management. These courses are aimed at individuals in senior positions, including those with the responsibility for training staff in their own countries. Particular attention has been given to the prevention, early detection and control of malaria epidemics. In 1996 WHO, in collaboration with other agencies, supported training of district health teams in epidemic preparedness and control in Nepal and India. More than 200 staff in India and more than 100 persons in Nepal were trained.

Following reorientation, malaria control in the countries of the Southeast Asian Region is now based on the application of targeted, site-specific, and cost-effective vector control measures in support of early diagnosis and prompt treatment of malaria disease. In practice, this means less reliance is placed on the use of insecticides for household spraying and there is a greater recognition than before of the importance of environmental sanitation measures to eliminate vector breeding sites.

Identification of high-risk areas in the countries of the region, based on a malariogenic stratification, has facilitated the targeting and choice of interventions. Thus, in tribal areas of India and Bangladesh which are refractory to transmission control, promotion of the use of impregnated mosquito nets has been made a main activity. Transmission control by selective insecticide spraying has been confined to areas with a high incidence of *P. falciparum* and significant malaria mortality, drug-resistant foci, development projects and epidemic-prone areas.

Environmental control is increasingly carried out in India, where the national malaria control programme was deploying, until recently, residual insecticides, including DDT and HCH, on a large scale. Recent large-scale studies in various parts of India has demonstrated that community participation can have a major impact on malaria control. In coastal villages of Pondicherry, malaria incidence was reduced by the manual removal of algae, which grows extensively on the water surface of various breeding places of *Anopheles subpictus*[23,24]. Community-based environmental interventions consisting of filling of low-lying mosquito breeding areas have been carried out in Gujarat state. In marshy and lowland areas, which could not be filled by soil, water-loving eucalyptus and poplar trees were planted by the communities[25,26]. As a result of these interventions, mosquito breeding declined considerably, which resulted in the reduction of malaria transmission[26]. In other areas, in addition to source reduction measures, the use of biological control methods has been introduced. Health education to increase community awareness of the risk of malaria and the role the community can play in its control was found to be an extremely important element in the success of this strategy.

The improved targeting of antimalaria operations appears to have resulted in an increased cost-effectiveness of the majority of malaria control programmes in the region. During 1992-96, the malaria situation improved in Thailand and Sri Lanka and the indigenous malaria-free status has been maintained in Maldives. The malaria situation remained static in Bangladesh, Bhutan, India and Indonesia. It has, however, deteriorated alarmingly in the eastern areas of Myanmar, bordering China, Thailand, and Lao Democratic People's Republic where transmission is intense, substantial population movements occur and malaria accounts for 30% of hospital admissions. Over 85% of the cases are due to multiresistant falciparum malaria. This epicentre of resistance to chloroquine, sulfa drug/pyrimethamine combinations, quinine and mefloquine is a major threat to neighbouring countries. Multidrug resistance is also a major problem in border areas of Thailand with Cambodia and in western Cambodia. A standard protocol for monitoring therapeutic efficacy of antimalarial drugs have been developed in joint consultations with programme managers from both the Southeast Asia and Western Pacific Regions and forms the basis of a widespread monitoring programme established in all countries of the Southeast Asian Region in 1997[27]

Western Pacific Region: Countries of the Western Pacific Region are in the process of implementing an accelerated programme of malaria control activities. Malaria control has been made a major priority in Cambodia, the Lao People's Democratic Republic, Solomon Islands, Vanuatu and Vietnam. Following the reorientation of the national malaria control programmes of the Western Pacific Region in 1991-93, morbidity and mortality due to malaria has been considerably reduced, e.g. the number of laboratory confirmed cases fell from 798,300 in 1991 to 621,191 in 1995. This was achieved through the employment of an integrated approach of intersectoral cooperation to support health service activities, involving education, public works and town planning departments. Community and individual participation also played an important role.

Malaria control interventions are being applied based on the knowledge of the local malaria epidemiology and on the availability of national and extrabudgetary resources. The main activities focus on early diagnosis and effective treatment and the protection of high-risk populations with insecticide-treated mosquito nets. Other vector control measures, such as house spraying with insecticides and environmental modification, are also being selectively applied to reduce transmission. House spraying is normally applied to curb malaria epidemics and where it can be cost-effective to protect those risk groups that cannot be protected by treated bednets or other measures. In high risk areas, house spraying may be the primary line of attack, and once a reduction of disease incidence is achieved, the bednet impregnation programme is deployed to maintain the gains achieved.

There has been a major impact of control measures on the malaria situation both in China and Vietnam. China has reduced malaria incidence by 92% during the last seven years. Whereas in Vietnam, the number of clinical and microscopically diagnosed cases and deaths was reduced by 46% and 92% respectively from 1991-95. These improvements are attributed to the large-scale use of artemisinin and its derivatives for treatment in multi-drug resistant areas and large-scale vector control with both pyrethroid-treated mosquito nets (7.9 million people protected) and indoor residual house spraying (4 million protected).

Countries of the Western Pacific share similar problems in malaria and its control with those of southeast Asia, especially in the border areas stretching from northeast India to Southern China. These problems relate to population movements across borders, the inadequacy of health services in these areas to prevent diagnose and treatment of disease, the improper use of antimalarial drugs, and the limited resources and operational difficulties in implementing control activities in these remote areas. As a consequence, the two regions face the most difficult problem of multi-drug resistance seen in the world today. However, reports have shown that the malaria situation is improving in some of these countries and the important lesson is that the constraints of drug and insecticide resistance, population movement are not intractable obstacles to malaria control if the right strategies are applied in the right way in the right place at the right time.

Perspectives for Malaria Control

The activities described above show that the first objective of the Action Plan that 90% of malaria endemic countries in the world will implement appropriate malaria control programmes by 1997 should be achieved by the end of the year. To achieve the second objective of the plans to reduce malaria mortality in 75% of malaria endemic countries by 20% by the year 2000 as compared to 1995, is a greater challenge.

Experience from several countries show that it is possible to reduce morbidity and mortality associated with malaria to acceptably low levels since malaria is still a preventable and curable disease. The investment of adequate human and financial resources is, however, crucial to success. While some countries are able to provide these resources themselves, external assistance is required in many cases.

The appropriation of funds by Ministries of Health for malaria control varies from one country to another, depending on the magnitude of the problem but primarily due to economic considerations. Most of the African countries are classified in the low economic development group and are going through major economic changes. Thus, even though malaria is recognized as a major health problem that impedes economic development, the scarcity of funds has prevented most Ministries of Health from launching effective programmes without major external assistance.

At present, the majority of the African countries do not carry out vector control but rely on disease management through the health services and on community-based interventions. The cost of these activities represents on average 10% of the total health expenditure. Since the coverage of the public health services is as low as 40% in most countries, a significant proportion of the population obtaining treatment outside the public services. Thus, the present level of national resources allocated to malaria programmes by the endemic countries does not match programme needs and is inadequate for undertaking effective and sustainable control programmes.

The annual cost of a "package" of basic essential activities for disease management, but excluding vector control, is estimated to be US $ 300,000 for each country, US $ 14 million per year for all countries or areas in Africa (South of the Sahara). In most cases, these costs cannot be covered by national budgets and will require external funding. These figures do not include the costs of epidemic detection and control, an increasing number of which are occurring in Africa. It is estimated that an additional input of US $ 1 million per year would be required for each country to carry out such an effective and sustainable programme, including a capacity for selective vector control. About 12 countries in Africa, in particular the ones with epidemic prone areas will be able to implement cost-effective disease management and prevention measures, given inputs for capacity building. It is estimated, therefore, that the external investments in malaria control in Africa within the next few years should be a total of approximately US $ 26 million per year. These costs do not include short-term technical assistance or international training but do include in-country training and operational research.

Outside Africa, the total population at risk is approximately 1,750 million. In these areas, countries are also showing an increased commitment towards strengthening malaria control programmes by mobilizing additional resources, e.g. India, Solomon Islands, Vietnam. India has probably the largest of all national programmes with an annual budget of more than US $ 40 million per year, covered mainly from national resources. The budget was increased by an additional 37% in 1995.

Based on these budget figures, it would appear that in countries outside Africa, malaria control programmes which include a capacity for diseases prevention have an annual public cost of between US $ 0.10-0.25 per person at risk, i.e. between US $ 175 million and 350 million per year. It would be reasonable to estimate that the external investments required for these programmes should be approximately 10% of the current public expenditures or US $ 20-35 million per year. Thus, it is estimated that the total external support for malaria control in the world required each year is between US $ 46 million and US $ 61 million. This support will need to be secured through bilateral or multilateral arrangements.

WHO continues to assist countries to mobilize external support and provides technical support within the limits of its resources. Although present external support to malaria control programmes is about 50% short of the required amount, recent developments in the obtention of additional external support are encouraging. For example, the Director-General of WHO has provided US $ 10 million for the acceleration of malaria control activities in 24 African countries in addition to US $ 0.10 million provided to African countries from the regular budget funds. The European Commission provided ECU 29 million for malaria control over a period of four years through bilateral agreements with the Governments of Cambodia, the Lao People's Democratic Republic and Vietnam in 1996. The World Bank has also demonstrated an increasing interest in support of malarial control and, at present, supports activities in countries such as Brazil, Madagascar and Vietnam. In addition, negotiations for World Bank support to malaria control in India are in their final stages. Other countries have received bilateral support from countries such as Australia, Belgium, Germany, Italy, Japan, the Netherlands, United Kingdom and the United States of America.

Apart from the external financial support needed for malaria endemic countries to achieve their objectives and targets, there is a need to further strengthen national political and budgetary commitments to malaria control to ensure proper resource allocation in the context of national health care and development planning. This will require not only the commitment of Ministries of Health but also other Ministries and the private sector whose activities may affect directly or indirectly the malaria situation. All possible intersectoral linkages will need to be established to ensure that the responsibilities of the malaria specialized services and the general health services are clearly defined, but also to ensure the avoidance of malaria resulting from human activities. The commitments to poverty alleviation, gender issues, children, emergency relief and environment of other programmes and organizations can be used as entry points for malaria control and to target vulnerable groups in greatest need. This will require the establishment of effective coordinating mechanisms within and between countries, the final responsibility for which can only rest with national authorities.

The involvement of the community in malaria control also has to be increased. More attention needs to be given to people's perceptions of malaria and of their health-seeking behaviour to ensure malaria-safe practices in communities and individuals, and to ensure the wider involvement of the community in determining priorities and in the allocation of the scarce health resources for malaria control. The decentralization of disease control and prevention services need to be continued since local conditions determine the most practical way to identify priorities and plan and implement appropriate interventions. The key for effective control is competent local action.

Whilst malaria is both a preventable and controllable disease and competent action can be taken with the tools available, research cannot be ignored as in the eradication era. All control programmes require a capability for operational research to address, not only the efficacy of specific interventions, but also social, economic, cultural and behavioural factors that affect malaria control. Resistance of parasites to drugs, of vectors to insecticides, and the need to improve diagnostic techniques show that research is also essential to the development of new tools for disease control and their deployment. National programmes and research institutes need to collaborate more closely to increase the relevance of research to malaria control.

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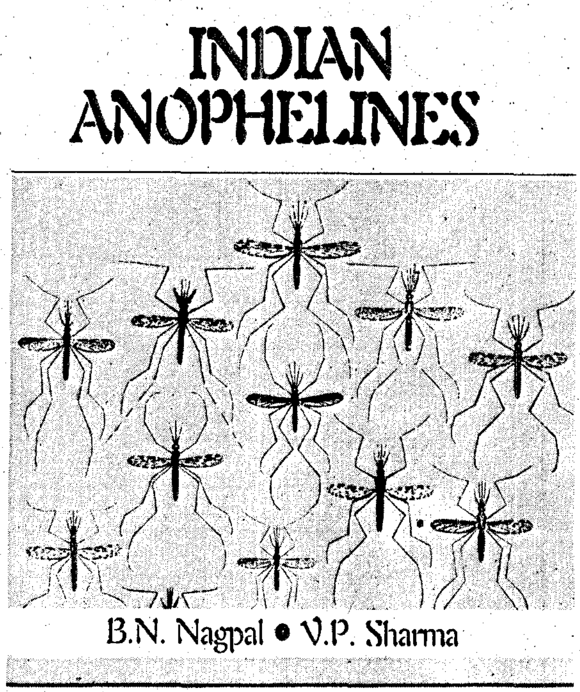

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