

Nobel Lecture

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The Treatment of Dementia Paralytica by Malaria Inoculation

Two paths could lead to a cure for progressive paralysis: the rational and the empirical. The rational path appeared to be practical, as since Esmarch and Jessen, in 1858, attention had been drawn to a connection between progressive paralysis and syphilis. If incontestible proof that progressive paralysis was a syphilitic brain disease was first given much later (I mention in this connection the names Wassermann and Noguchi), therapeutic attempts to apply anti-syphilitic treatments were nevertheless instituted much earlier.

Established psychiatry, it is true, soon turned away from the specific therapy. In all the textbooks it was stated that the mercury cure was of no use against paralysis and was usually harmful.

However, systematic research on this point was not undertaken. It appears that the demand made by Jadassohn in 1912, that "one must compare, one with the other, a large series of cases untreated and of cases energetically treated with mercury", was nowhere put into effect.

When rather belated Runge-Kiel in 1914 established that among 555 paralytics collected between 1901 and 1912 there were remissions in 3.9% of the untreated cases, 9.3% of those treated with iodine, and 11.4% of those treated with mercury it was still not possible to say that the iodine-mercury treatment was completely ineffective. However, its effect was unsatisfactory and, with rare exceptions, not lasting.

The discovery of arsphenamine (Salvarsan) by Ehrlich brought new hope. The disappointment which soon followed was due to quite insufficient dosages. As one reads the reports of writers who have given arsphenamine in large doses and in rapidly repeated courses of treatment, and when one hears of the remissions obtained, in number and in duration far superior to the number of remissions observable in untreated paralysis, it cannot confidently be maintained that arsphenamine is ineffective against progressive paralysis. Yet it seems indeed, disregarding rare exceptions, that sooner or later a point is reached where arsphenamine treatment is unable to halt the fatal progression. The augmentation of the treatment by the employment of bismuth preparations could not change this.

There are, however, still always writers who expect the cure of paralytics from specific treatment alone.

But the question is not one of prestige between specific and non-specific treatment, but of what is the most far-reaching therapeutic effect on the disease obtainable.

And thus we have arrived at the empirical method.

Progressive paralysis has always been regarded as an incurable disease leading within a few years to insanity and death.

Nevertheless there were records of cured cases of progressive paralysis; cases in which there was such a complete retrogression of all the symptoms of the disease that it was possible for the person concerned to go about his life and business independently for many years. And even though such cases were extraordinarily rare, there were still relatively frequent remissions of a considerable duration in which the symptoms of the disease already developed retrogressed to a greater or less extent. Thus, in principle at least, progressive paralysis was necessarily a curable disease. And Francis Bacon, Lord Verulam, had already pronounced that it must be of the greatest interest for the physician to study healed cases of incurable diseases.

Now, the observation has been made that, in the rare cases of cure and in the frequent remissions of progressive paralysis, a febrile infectious disease or protracted suppuration had often preceded the improvement in the state of the disease.

In that lay a pointer. These cures following febrile infectious diseases, of which I had experienced striking instances myself, led me to propose as early as 1887 that this natural experiment should be imitated by a deliberate introduction of infectious diseases, and I suggested at that time malaria and erysipelas as suitable diseases. I singled out as a particular advantage of malaria that there is the possibility of interrupting the disease at will by the use of quinine, but I did not then anticipate to what degree these expectations from induced malaria would be fulfilled.

At that time I did not proceed to the direct application of these proposals, apart from an unfortunate experiment with erysipelas, and I also hardly had the authority then to carry on with them.

On the other hand I attempted to imitate the action of a febrile infectious disease by the use since 1890 of tuberculin which Koch had just introduced. At first this was used not only in progressive paralysis, but also in other mental disturbances, not infrequently with beneficial consequences. (This was to some extent a forerunner of the use of protein therapy, which later attained a great advance.) As there were among these, some cases of progressive paralysis, my interest soon concentrated on this disease because a favourable result cannot be so easily regarded as fortuitous as in other psychoses.

It was ascertained by means of a preliminary experiment of a large number of paralytics that those treated with tuberculin (with a maximum dose at that time of 0.1) showed more and longer-lasting remissions and a longer duration of life than an equal number of untreated paralytics. Afterwards, this treatment was carried out systematically and with an increasing dose of tuberculin (up to 1.0), and simultaneously a vigorous iodine-and-mercury treatment, later accompanied by arsphenamine injections, was also introduced.

In 1909, at the International Medical Congress in Budapest I gave some information on these methods of treatment, which were thus the first combined treatment - i.e. specific and non-specific - of a syphilitic disease.

Qualitatively the remissions which were obtained by means of the mercury- tuberculin treatment did not differ from those to be attained through induced malaria. The complete disappearance of the mental disturbances and the resumption of business activity, even in professions which make greater intellectual demands - such as civil servant, officer, barrister, solicitor, teacher, industrialist, actor, etc. - and the duration of the remissions was in individual cases quite remarkable; amounting to up to fifteen years.

But the number of relapses was great, the lasting remissions were in the minority.

I attempted to increase the effectiveness of the non-specific treatment by the utilization of various vaccines - staphylo-streptococcal vaccine, typhus vaccine - without altering the frequency of discouraging relapses in the slightest.

In the course of this experimentation with treatments I was able to observe repeatedly that particularly complete and long-lasting remissions presented themselves precisely in those cases in which an unintentional infectious disease, such as pneumonia or an abscess, appeared during the course of the treatment.

In 1917, therefore, I commenced to put into practice my proposal made in the year 1887, and I injected nine cases of progressive paralysis with tertian malaria.

The result was gratifying beyond expectation: six of these nine cases showed an extensive remission, and in three of these cases the remission proved enduring, so that I was able to present these cases of cured patients who have without interruption taken up again their former occupations, to this year's annual meeting of the German Psychiatric Society as having been able to follow them for ten years. After the result of this first experiment was pursued for two years, I went on, in the autumn of 1919, to continue this experimental treatment on a large scale, and I made a report on it in 1920 to the annual meeting of the German Psychiatric Society in Hamburg.

Whereas the earlier non-specific methods of treatment of progressive paralysis had met with little approval, it was otherwise with the malaria treatment. After Weygandt and Nonne, stimulated by Mühlens in Hamburg, had first tested the method of treatment on a large number of patients, it found quick acceptance in many psychiatric clinics and insane

asylums, and is currently used, as far as I am informed, in all the countries of Europe, in North and South America, in South Africa, in the Dutch East Indies, and in Japan.

The overwhelming majority of writers agree that with this method remissions can be obtained which are on a scale far exceeding those attained by any other method.

Nevertheless, the malaria treatment should not simply replace specific treatment but should be used in conjunction with it. Some writers believed at first that they could dispense with the specific treatment, in that they obtained brilliant remissions by malaria alone. But the question is how to obtain the maximum therapeutic effect from the treatment. So, I undertook comparative investigations in which paralytics admitted to the clinic were treated alternately, the one with malaria only, the other with malaria followed by nearsphenamine. The superiority of the combined specific-non-specific treatment was clearly shown.

The cases which had been subsequently treated with nearsphenamine had 48.5% full remissions, those with no subsequent treatment only 25%. On the other hand, the number of deaths in the latter group was higher - 18.7% against 12% - and likewise the number of rapidly deteriorating cases was 22% against 6.7%.

The malaria treatment is thus to be associated with a specific treatment. Insofar as nearsphenamine is concerned, the drug should be given first after the fever has subsided, as otherwise the malaria is cut short. In my clinic now 5.00 grams of nearsphenamine are given over six weeks after each malaria treatment.

Malaria treatment is the more effective the earlier in the course of the paralysis it is carried out. Therefore it is impossible to get a correct picture of its potential effectiveness by simply calculating that out of such and such a number of paralytics treated with malaria so many per cent obtained complete remission. It depends very much on how many among the material in question were in the initial stages of paralysis and how many were in the advanced stages.

We have therefore for some time singled out from the first, those cases of paralysis on their very first arrival at my clinic which from the degree and duration of their illness promised a favourable outcome and followed their progress separately. It was shown, that of these cases 84.8% obtained a full remission and 12.1% a partial remission, and that out of the total number of this series only one in thirty-eight had to be committed to the asylum.

Hence it was shown that progressive paralysis is, in principle, curable and that the practical success of the malaria treatment will be the greater the earlier the diagnosis of the illness is established - the more, that is, that the early stages of paralysis are recognized by physicians. It has become apparent that it is unwise to employ other methods of treatment against paralysis before the malaria treatment, as this means time wasted.

As the malaria treatment is the more effective the earlier it is employed, it would thus be best if it were carried out immediately on thoseluetics who are threatened with progressive paralysis. Whichluetics are these? We know that they are thoseluetics in whom the cerebrospinal fluid in the advanced period of latency gives a positive reaction.

It is due to the late Kyrle of Vienna that the malaria treatment was extended to theseluetics in that in these cases, which are not yet immediately threatened, he prescribed a course of arspenamine to precede the malaria, and a second course to follow it. The results in respect of the readjustment of the cerebrospinal fluid, which in such cases with other methods of treatment is on the contrary frequently very refractory, were so gratifying that already a large number of syphilologists have become acquainted with these methods. And it is to be hoped that once these methods become public property, psychiatrists will have very much fewer paralytics to treat.

That the malaria treatment attained so great a dissemination is due to some favourable results, only apparent during its application, which could therefore not been expected from the beginning.

It would have been difficult in many places to continue the malaria treatment if it had not been possible to maintain for an unlimited period a malaria strain by continual passage through human beings - that is in the asexual cycle. This was at first doubted, or at least the feat was stated, that such a strain would, in the course of its passage, change its properties, i.e. might become either no longer infectious or too virulent. These fears have proved groundless. In my clinic there is a malaria strain in use that since September 1919 has made about two hundred passages through human beings, without its infectiousness, its virulence, and its therapeutic properties having been altered. Similar experiences have been had in many places.

The uninterrupted breeding of such a strain is, however, only possible where there is access to a sufficiently large number of paralytics needing treatment and possibly also ofluetics in the advanced latency.

In places with little patient material, however, such a strain of induced malaria will always die out again, and it would involve great and often insurmountable difficulties to always procure a new case of natural malaria again to start a treatment, for the malaria virus will not breed in cultures.

Fortunately, however, the malaria parasites in human blood remain infectious for some time outside the human body, and this capacity can, by special methods of preservation be maintained for up to three days and in rare exceptions even longer, so that it is possible to send the virus over considerable distances by various means of transport.

It is therefore possible to supply with malaria virus an area of a very large radius from a centre, especially if use is made of the most modern form of transport, air mail. In this way we once successfully supplied malaria blood to Constantinople from Vienna.

It was finally a fortunate circumstance, which was not expected from the first, that tertian malaria brought on by injection proved to be so extra-ordinarily sensitive to quinine that a few grams of quinine suffice to cure the malaria completely and permanently, so that there is no fear of a relapse. It was through this that the great expansion which induced malaria has gained was first made possible.

When tertian malaria is acquired naturally the attacks of fever may also be cut short very effectively with quinine, but the patients remain carriers of the plasmodium and frequently relapse sooner or later. How would it have been possible to release so many paralytics and advanced syphilitics from the hospitals when outside they first of all ran the continual risk of a relapse and secondly, particularly where there were anopheles, were a danger to their environment?

The patient inoculated with malaria who has been adequately treated with quinine neither endangers himself further (in the sense of a malaria relapse), nor can he endanger his environment. However, he can from the moment of infection up to the elimination of the malaria present a danger to his environment, as malaria can be transferred from him to other persons through the sting of the anopheles, and that is then not induced malaria, but natural malaria, with its resistance to quinine.

This danger, which was assumed with the presence of anopheles in places of treatment, can be excluded with a fair degree of safety, if the patients are kept under mosquito-proof netting during the whole duration of the treatment. This has been done in several countries, such as England and Sweden.

The question is whether it is not possible to meet this danger in yet another way. An experiment was made in my clinic in 1924 with a large number of patients and mosquitoes to see if induced malaria could be transferred to other patients through anopheles; the experiment was without results. Such transfers have, however, been obtained by other writers, notably Shute and James, and also Warrington Yorke, in England, have carried out numerous successful transfers of induced malaria by means of anopheles. The Vienna strain has, however, been proved at that time to be free of gametes by an experiment of the Italian malariologist D. Vivaldi. The strains which were transferable through anopheles have all proved to be gamete producers; and the English writers mentioned in particular state that the transference by anopheles is the easier, the richer in gametes the donor's blood is.

Plehn and Schulze of Berlin, and Vonkenel of Munich, also reported on such gamete-free strains.

I have therefore in the preceding year made the demand that everyone who practises malaria therapy, should procure a gamete-free strain and thus eliminate the danger of a transfer by means of anopheles.

More recent investigations carried out in my clinic this year have, however, shown that this demand cannot be realized, as gamete-free malaria strains cannot be obtained by

transferring preserved blood unaltered from one place to another. That is to say that it has been shown that from the moment malaria blood leaves the human body, the malaria parasites deviate from the normal course of development; they leave the red blood corpuscles and assume gametic forms.

We thus have in the preserved blood, not a gamete-free strain, but predominantly gamete-containing injection blood.

Thus the propagation of a gamete-free strain would not be possible with preserved blood but only by direct transfer from one patient to another. It would not be possible to effect this by transferring the blood but only by transferring the patients.

Induced malaria is, however, of itself a dangerous disease. The attacks of fever usually reach 40°C by the third attack. The temperature often remains above 40°C for many hours in the later attacks. It frequently reaches 41°C. The highest temperature that I have observed was 42°C. In addition, the attacks frequently assume the quotidian type or take that course right from the beginning. It appears, incidentally, that paralysis plays a role in the appearance of the quotidian type, as in luetics of advanced latency the malaria usually remains tertian. Perhaps in this respect, however, different strains of malaria behave differently, since Bravetta in Novara has at his disposal a strain of which he reports that it causes without exception attacks of the tertian type.

The high temperatures on the one hand and the brief pauses in the quotidian type on the other, make on the usually already weakened organism of the paralytic, especially on his heart, often too great demands; and thus we and others also have seen not by any means infrequent cases of death during the fever period or immediately afterwards.

However, by various measures, this danger has been decreased to such an extent that fatal cases are now almost never seen. We use several methods to this end. Something can frequently be effected by the mode of inoculation. That is to say that, if one inoculates intracutaneously with a small quantity of blood, about 0.1 cm³, the fever usually develops into the tertian type, especially when the blood groups of the donor and recipient correspond, and the avoidance of the quotidian type is already an alleviation.

In other cases we mitigate the fever with small doses of quinine (0.2-0.3) which must not, however, be given two days in succession, otherwise the fever ceases entirely. After a single administration of such a dose, the fever disappears for some days, during which the patient recovers; and when the fever sets in again it runs a milder course, as a rule. Alternatively one gives 0.1 quinine every two or three days from immediately after the injection, and in this way obtains a general alleviation of the course of the fever.

Finally, in cases which on account of their physical constitution or on account of their age - somewhere between 55 and 70 - appear particularly endangered, a division of the course into two parts has been proved particularly successful. In such patients the fever will be interrupted by quinine after two to at the most four attacks. This is followed by a six weeks' pause taken up with injections of nearsphenamine, after which the patient will be

infected a second time. He has meanwhile recovered, and now endures the continuation of the cure very well.

In this connection the question also arises, how many attacks of fever are necessary for a successful malaria cure? This can only be decided by experience, as we have no biological evidence as to when the optimum activity occurs. In my clinic the fever is, as a rule, terminated after eight attacks. English writers, by comparing therapeutic results after a shorter or longer duration of the fever period have likewise come to the conclusion that the optimum therapeutic effect lies at around eight attacks.

Some writers have let their patients have very much longer fevers. However, I believe that it is much better to give to a patient in whom a course of some eight attacks of fever has had an unsatisfactory result, a second course soon afterwards, than to endanger the reconstruction which should follow each malaria injection by weakening the patient too severely by continuing the course too long.

This reconstruction as an aftereffect of induced malaria, and the long duration of its aftereffect in general, is something that must be taken into account by every explanation of the mode of action of induced malaria.

The improvement in the physical and mental health of the patients is not as a rule demonstrable immediately after the last attack of fever and never to the full extent. On the contrary, it often happens that a paralytic who on completion of the treatment has been committed to the asylum as uncured, presents himself again after six or twelve months and states that he has taken up his occupation again.

The most convincing, because numerically demonstrable, expression of this delayed action of induced malaria is in the reactions of the serum and of the cerebrospinal fluid. The immediate effect of the malaria treatment on these reactions is negligible, and the changes do not run parallel with the clinical symptoms. It does change however, if these reactions are repeatedly investigated at intervals.

Kyrle has already noticed that in the malaria treatment of advanced syphilitics distinguished by a positive cerebrospinal fluid, the immediate effect of the treatment was relatively small. However, after the space of a year the cerebrospinal fluid was negative, although since the malaria, no further treatment had taken place, and in spite of the fact that before the malaria treatment the most vigorous specific therapy had been applied without any result.

The same thing happens with paralytics, only at an even slower tempo. In them the negativity of the cerebrospinal fluid reactions often first appears two, three, and even four years after the malaria treatment and still without any specific or non-specific treatment being introduced after the latter.

My assistant D. Dattner reported three years ago on the results of treatment from a particular aspect on a series of 129 paralytics treated with malaria in the period between

the beginning of 1922 and the beginning of 1924; 66 of them underwent cerebrospinal fluid examinations at more frequent intervals up to the present day. They were thus cases in whom the malaria treatment lay about three to five years behind. Of these cases, repeated examinations of the cerebrospinal fluid in 1927 showed completely negative findings in 36, and nearly negative findings in 23. This favourable result, however, had first appeared in many of them two or more years after the cessation of the malaria treatment and without any further treatment having been administered in the meantime.

It has been shown by these investigations that the serum reaction is more refractory than the cerebrospinal fluid reaction.

The regularly repeated examination of the serum and cerebrospinal fluid also provides good evidence to establish a prognosis for the remissions achieved. Relapses, that is, do occur, but they form by far the minority beside cases which have attained a full remission. However, the cases in which this progressive improvement in the cerebrospinal fluid appears, do not relapse; but the contrary does not hold good. Curiously enough, this progressive improvement of the cerebrospinal fluid appears also in a number of the cases which do not improve clinically. It is thus of prognostic value only in conjunction with the clinical findings.

How is the action of induced malaria on the paralytic process to be explained?

It is certain that it is not the high temperature alone that is effective. The spirochaetes, it is true, disappear from the brain during the fever. When, however, the fever has passed, they are immediately to be found again in the brain, at least in cases where the course is not successful, as Forster has shown. Where are they in the meantime? Does malaria act against syphilis in general or predominantly against progressive paralysis? We know that syphilitic processes in the secondary period are also influenced by malaria, yet this action appears to be less permanent than the action on progressive paralysis. Vascular syphilis appears to be less favourably affected than progressive paralysis. Further, it has been experienced that soon after the malaria treatment gummata appear, even in cases in which the paralytic process has been favourably affected.

It appears then, that malaria besides a non-specific action against the syphilitic infection, also exerts a specific elective action on the cerebral process of progressive paralysis, including advanced infection of the cerebro-spinal fluid.

It is also very likely that malaria creates favourable conditions for all reparatory processes because of its cyclic course, and because ultimately a rapid transition takes place from a serious state of illness to a full recovery. The superiority of induced malaria over the different types of stimulation therapy, e.g. by the injection of vaccines and proteins, has been shown by Schilling and his colleagues on the cytological blood-picture, and by Donath and Heilig on the chemical blood-picture. It is certain that induced malaria therapy will yet pose many worthwhile problems for research to explain.

From [Nobel Lectures](#), *Physiology or Medicine 1922-1941*, Elsevier Publishing Company, Amsterdam, 1965

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