

men who were fortunate enough to become intimately associated with him.

Under Dr. Hewlett's direction the Department of Medicine at Michigan continued to grow and made marked and well recognized advancement. Under his leadership valuable contributions to scientific medicine were made.

Later he was called to the home of his boyhood, to become Professor of Medicine at Leland Stanford University in California. Here he continued this valuable work as a physician, teacher and investigator.

Dr. Hewlett possessed not only an unusual intellectual equipment and ability as an investigator, teacher and physician, but also a most attractive personality. Quiet and thoughtful, and giving the impression of much reserve power and force, yet he was a most interesting and agreeable companion. All the members of the early group comprising this society were his personal friends. He was always interested in the younger members of this society and many of them were guided in their later careers by his writings and by his personal influence.

The profession of medicine has lost in Dr. Hewlett one of its ablest and most valuable members; this society has lost one of its wisest and most capable counselors.

But we have lost much more, we have all lost a sincere and true friend. It is therefore especially fitting for this society to record our admiration for Dr. Hewlett as an able scientist, our appreciation of him as a wise and skillful physician, and at the same time express the personal affection which all of us had for him as a fellow worker and a friend.

PRESIDENT'S ADDRESS

MALARIA: SOME INTERESTING OBSERVATIONS RELATIVE TO MALARIA THAT HAVE BEEN MADE IN THE TREATMENT OF GENERAL PARALYSIS BY INOCULATION WITH MALARIA PLASMODIA

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In 1917, Wagner von Jauregg (1) first reported the treatment of general paralysis by inoculation with malaria. Favorable results were obtained in six of the nine cases, three of which were later re-

ported to be still actively at work, after four years. In 1922, he reported more than 200 cases treated by this method, over 50 of which showed remissions sufficient to permit the majority of them to resume their former occupations. His early report was followed by reports of other observers in Germany and Austria particularly, but still later in several other countries (2) (3) (4) (5) (6) (7). Reports of apparently favorable results in this disease, for which no satisfactory treatment had been available hitherto, have led to an ever increasing employment of this method until at the present time the literature contains reports of a few thousand cases. Most of the reports indicate favorable results in a proportion of cases ranging from almost none up to as high as 88 per cent (8).

On the whole, the results published are most encouraging. However, still more time and experience may be necessary to show how much allowance should be made for over enthusiasm in the use of a new and somewhat spectacular method of treatment and the difficulty of controlling the personal factor in the interpretation of the clinical state, especially in nervous and mental diseases. This applies particularly to syphilis of the nervous system in which the condition is chronic. The progress is often extremely slow; there are spontaneous improvements and the symptomatology is such that one is easily led astray. There is great danger of misinterpreting slight remissions as arrest and of attributing apparent results to treatment when they would have occurred otherwise.

Whatever therapeutic value this method of treatment may prove to have, the deliberate inoculation of hundreds and even thousands of patients with malaria under favorable conditions of control, in many particulars at least, has afforded an opportunity for observations upon certain features of malaria, far greater than had previously existed. These observations have served to emphasize certain facts in regard to malaria which were already well known but perhaps not so thoroughly appreciated and also to bring to light other facts about which much less was known. Since the observations with regard to malaria were made incidentally in most instances, when the main objective was treatment of another entirely different disease, they are probably less influenced by pre-formed ideas. My purpose is to call attention briefly to some of these points which may be called by-products of clinical investigation of the treatment of general paralysis.

Method of inoculation. Blood drawn from the vein of a malaria subject has been injected intramuscularly, subcutaneously or intravenously. Inoculation directly into the blood stream is somewhat more certain to infect, although both subcutaneous and intramuscular inoculations are nearly always successful. Injection of blood immediately after withdrawal gives best results, but citrated blood has been used successfully in some instances several hours after its withdrawal. In one instance (9) defibrinated blood was kept 'on ice' for 65 hours and used successfully. By keeping it on ice, it has retained its infectivity after transportation over long distances. Inoculation by the bites of infected mosquitoes has been employed, but it has been found that on the average, cases inoculated in this way, are much more difficult to cure of their infection permanently. In one instance reported by Davidson (10) of 23 mosquito infected cases, 56.5 per cent relapsed after 30 grains quinine daily for 3 days, whereas of 33 inoculated cases only 3.3 per cent relapsed. Many others have noted the infrequency of relapse of inoculated cases of malaria. One of the facts that seems to be established by these studies is that passage of malaria parasites through the sporozoite cycle in the mosquito increases their resistance in the human body.

Incubation period. The incubation period, measured by the appearance of parasites in the peripheral blood and the occurrence of fever, varies according to the mode of infection. It averages about fourteen days following infection by mosquitoes, a little longer following intramuscular or subcutaneous inoculation, and about seven days following intravenous inoculation. Clinical symptoms do not seem to be influenced by the mode of infection.

Different strains. Considerable variation in different strains of the same variety of parasite with regard to the height of the temperature has been found. For instance, Bunker and Kirby (11), using two different strains of *P. vivax*, found with one that the temperature reached 105°F. in 23 per cent of the cases, while with the other, 86 per cent reached this temperature. Only 3 per cent of the cases inoculated with one of the strains reached 106°F., while 64 per cent of the cases inoculated with the other one reached this height. Other effects, such as jaundice and anemia, are much more marked from certain strains than from others of the same variety of parasites.

Immunity. Although it has been possible to infect nearly all cases, a few have been found that seem not to be susceptible. Bunker and Kirby (11) cite one patient who failed to acquire malaria after four widely separated intravenous inoculations, although other patients inoculated with the same blood at the same time developed the disease in the usual manner. A good many cases are also reported where patients who had recovered from a successful inoculation, either spontaneously or as the result of treatment, were immune and could not be infected again. Acquired immunity therefore exists, although rarely.

Spontaneous recovery. A great many cases reported have lost their infection and entirely recovered after only a few paroxysms, without any quinine or other treatment. This often occurs in the same way in naturally infected persons, as is well known to those who are familiar with malaria. In fact, in regions where malaria is very prevalent, there are a great many infected persons who have few or no symptoms, although parasites in their blood are easily demonstrated. Spontaneous recovery occurs in many of these and this is followed by more or less immunity from subsequent infection. However, we have shown (12) several years ago that whatever immunity follows spontaneous recovery is probably of short duration.

Effect of treatment. The effect of treatment in these inoculated cases of malaria under favorable conditions for observation has been impressive and is probably the most important fact from a practical standpoint that has been brought out. The experiences reported emphasize the effectiveness of quinine in the treatment of malaria and indicate that the large amount often given to malaria patients is unnecessary. The treatment used by the different observers has varied considerably, ranging from 5 to 30 grains quinine (usually by mouth) daily for periods of from three days to two weeks and occasionally, but rarely, longer. Among the three or four thousand cases reported, the clinical attacks were promptly controlled, usually within 24 hours and always within two or three days. This is in line with the experience of many students of malaria to the effect that attacks of this disease are always promptly controlled by the use of moderate doses of quinine.

Clinical investigation or clinical research, the encouragement and

promotion of which is the object of this Society, has, in this instance, not only furnished information relative to what it now seems may be a valuable therapeutic agent for general paralysis, but at the same time it has shed new light on the entirely unrelated disease, malaria, and has impressively emphasized certain previously known facts relative to this disease.

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The Relative Importance of the Systolic and Diastolic Blood Pressure in Maintaining the Coronary Circulation. By FRED M. SMITH and (by invitation) G. H. MILLER and V. C. GRABER, Iowa City.

The object of the investigation was to determine the effect of specific changes in the systolic and diastolic blood pressure on the coronary circulation.

Dogs were employed. They were anaesthetized and the blood pressure from the carotid artery was registered on the kymograph by a Straub membrane manometer. The chest was opened and a Morawitz-Zahn cannula was introduced into the coronary sinus. The blood was prevented from coagulating by heparin. The blood from the coronary sinus was collected in a 50 cc. graduate, and the amounts were registered on the kymograph. The blood was maintained at a constant temperature and reintroduced into the femoral vein. Changes in the systolic and diastolic pressures were induced by constricting the thoracic aorta, and by experimentally produced arterio-venous aneurysm and aortic regurgitation.

When the thoracic aorta was constricted by an adjustable clamp, it was possible, within certain limits, to increase the diastolic pressure without altering the systolic pressure. The coronary flow was increased in proportion to the elevation of