PROBLEMS OF PYRETOTHERAPY IN PARALYTIC DEMENTIA.

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Pyretotherapy, or the artificial induction of pyrexia as a means of treatment of the psychoses, has engaged the attention of psychiatrists for many years. The means employed to this end have been numerous, and they may be divided into two classes:

1. Chemical: Hypodermic injections of sodium nucleinate; or of protein in the form of peptone, blood, milk, tuberculin or emulsions of dead bacilli.

2. Infective: The introduction of living organisms, especially *Plasmodium vivax malariæ* and *Spirochæte recurrentis duttoni.*

When the rise of temperature is induced chemically, few physical signs are detected beyond leucocytosis and pyrexia, whereas, when the infective means are employed, many of the signs which constitute the syndrome of fever, for instance, heat and dryness of the skin, tachycardia, increased respiratory rate and diminution of the volume of the urine, with heightened colour, retention of chlorides and increased excretion of urates, occur.

Pyrexia is only one physical sign in the syndrome of fever.

The application of pyretotherapy to paralytic dementia is largely empirical. It is a surprising fact that whereas the literature on the subject deals exhaustively with the clinical results of treatment and the changes which are found in the brain, attempts to explain the rationale of this form of therapy are scanty. It is the object of this thesis to inquire into the rationale through consideration of—

1. The part played by the reticulo-endothelial system in the genesis and control of pyrexia.

2. The changes which are found in the hæmatopoietic tissues in paralytic dementia.

3. The effect of pyretotherapy upon the reticulo-endothelial system and its relationship to the changes found in the blood-forming tissues in paralytic dementia.

The inquiry outlined above was suggested to the writer by the systematic investigation, over a period of four years and involving a thousand histological examinations, of 67 cases of untreated

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paralytic dementia and 21 of non-paretic syphilis, in which it was found that, in the former, definite changes in the bone-marrow and blood constantly occurred, which were absent in the latter.

Finally, 500 examinations were made with regard to the changes in the blood-cells in 28 cases of paralytic dementia treated with relapsing fever, and in 4 treated by injections of foreign protein.

Summary of Recent Literature.

1. *The Pathogenesis of Paralytic Dementia.*

Many theories have been invoked to explain why some subjects of syphilis develop paralytic dementia while others do not.

Dujardin and Targowla (1) consider that the disease is the outcome of an abnormal prolongation of the anallergic period of the primary and secondary stages of syphilis, in which the tissues of the body have not yet become sensitized to the virus, while in non-paretic syphilis the tertiary stage is an allergic one of marked reaction to the antigen, in which the vascular changes, allowing greater permeability, permit the production and dissemination of antibodies. They mention, in support of this, that paretics react but little to intradermal injections of protein, while patients in the tertiary stage of syphilis react well.

With regard to malarial treatment, these authors consider that the malarial infection induces an allergic state in which a defensive reaction is set up against the malarial infection, the fate of which is shared by the syphilitic virus. If malaria indeed induces some state of resistance to the syphilitic processes at work, then we have an explanation of why the Wassermann reaction in the cerebro-spinal fluid is mitigated in intensity in the course of a year or two, or, in rare cases, intensified immediately after treatment. No reference, however, is made to the part played in the production of bodily resistance and immunity by the reticulo-endothelial system, especially by those portions which are included in the spleen and marrow. Finally they do not explain why the neural elements should be particularly vulnerable to the syphilitic virus in those patients who develop paralytic dementia.

An opposite view is propounded by Fildes and McIntosh (2), who consider that all tertiary and parasyphilitic lesions are the result of hypersensitiveness in certain tissues which produces what they describe as an allergic reaction, resulting, in the case of paralytic dementia, in death of the nerve-cells and proliferation of the neuroglia.

Collier and Adie (3) advance arguments against the theory that there are two varieties of *Spirochæte pallida*, a neurotropic and a

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dermatropic—a theory which finds little support. The same authors associate themselves with the view, widely held, that all forms of syphilitic affection of the central nervous system start as meningo-vascular disease and that the nerve elements are affected later.

Bolton (4) considers that paralytic dementia will only appear in brains the subject of some constitutional defect. In other words, the subjects of paralytic dementia would, if they had not contracted syphilis, have been liable ultimately to some other form of dementia.

2. *The Effects of Pyretotherapy.*

Sabastiani (5) found that in untreated paralytic dementia leucopenia occurred, accounted for by diminution in the number of neutrophilic leucocytes, while in non-paretic syphilis there was a neutrophilia. He considers that in paralytic dementia the spirochæte has a special action upon the reticulo-endothelial system.

The cell-changes which occur in the blood of paretics treated by induced malaria are described in detail by Paoletti (6). He discusses the *rôle* possibly played by the various types of leucocyte, but he offers no suggestion regarding the blood-forming tissues. He refers to the "shift to the left" in the Arneth count and he quotes Wolf Skalweit (7) on the same subject.

Saunders (8) mentions the "shift to the left" in untreated dementia paralytica, and states that it is corrected by malarial therapy.

Bruetsch and Bahr (9) and Freeman (10) describe the histological changes which take place in the brain after malarial treatment. They find increased perivascular infiltration by mononuclear and plasma-cells during the malarial paroxysms. They describe, after the termination of the fever, the disappearance of the perivascular infiltration, the return of the perivascular lymph-spaces to their normal condition and the reappearance of the cortical lamination. They suspect that the plasma-cells, which were so prolific in numbers during the malarial paroxysms, are withdrawn into the blood-vessels in order to reinforce the phagocytic action of the monocytes in the blood.

Hattori (11) demonstrated the presence of plasma-cells in the blood of paretics undergoing malarial treatment.

The only direct reference to the reticulo-endothelial system is made by Bruetsch and Bahr (9), who describe proliferation of this tissue, especially in the cerebral vessels, spleen and periportal spaces of the liver. They consider the question from the point of view of the resistance to the malarial infection and its secondary

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effects upon the syphilitic process, and ignore the influence of the reticulo-endothelial affection upon the pathogenesis of paralytic dementia or its relationship to the rationale of treatment.

Sträussler and Koskinas (12) consider that the diffuse inflammation of the brain and meninges, characteristic of paralytic dementia, is converted by means of malaria into a more localized gummatous type resembling cerebro-spinal syphilitic meningitis.

Before proceeding to a description of a series of cases it is advisable to consider certain aspects of the genesis and control of pyrexia and fever, for the following thesis will maintain that syphilitic involvement of the reticulo-endothelial system, resulting in the depression of some of its functions, is one of the factors which determine whether a given syphilitic subject will develop paralytic dementia. Since most causes of pyrexia, especially those which produce the most beneficial therapeutic results, stimulate this tissue, it follows that stimulation of the functions of the reticulo-endothelial system other than by the mere production of a rise of temperature constitutes part of the rationale of pyretotherapy, since the results achieved by pyretotherapy, through stimulation of the leucoblastic tissue in the bone-marrow and the reticulo-endothelial tissue in the cerebral vessels, consist in either the conversion of paralytic dementia into meningo-vascular syphilis or in simple retrogression of the characteristic pathological changes.

The Reticulo-Endothelium and Pyretogenesis.

The mechanism whereby the temperature of the body undergoes its normal variations in health and its fluctuations in disease is little understood. Many theories have been advanced, the most widely accepted being that the temperature at any given moment is the resultant of the interplay between heat-loss and heat-production, the two being ultimately regulated by the central nervous system. Consequently, one of the two factors being constant, changes in the other will be associated with alterations in temperature.

None of the theories takes into account the possibility that the reticulo-endothelial system may play an active part in the production and control of pyrexia. Yet pyrexia is almost invariably accompanied by cytological changes in the peripheral blood in the form of numerical changes in the white corpuscles.

The more usual causes of pyrexia are as follows:

(*a*) *Associated with Fever.*

Bacterial and protozoal diseases.
Septic infections.

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(*b*) *Not associated with Fever.*

High external temperature in moist medium.
Muscular exertion.
Toxic substances:
- Atropine.
- Strychnine.
- β-tetrahydronaphthylamine.

Lesions of central nervous system:
- Cerebral hæmorrhage, rarely.
- Lesions of pons.
- Lesions of spinal cord.
- General paralysis.

Affections of hæmatopoietic tissues:
- Pernicious anæmia.
- Leukæmia.
- Chloroma.
- Aplastic anæmia.
- Hodgkin's disease.
- Secondary anæmia, following repeated hæmorrhages.
- Fractures of bone.
- Neoplasm of the marrow.

In the first group it will be observed that all septic or infective diseases are associated with either an increase or diminution in number of one or more varieties of leucocyte. It follows that the hæmatopoietic tissues are stimulated by some diseases and depressed by others.

In the second group, diminished loss of heat is chiefly responsible for the effects of exposure to a high temperature. In sun-stroke the rays of the sun are considered to exert a chemical effect, and it will be remembered that leucocytosis may occur, showing that the reticulo-endothelial system takes part in the somatic reaction. During muscular exertion there is a slightly increased output of both red and white cells. It is interesting to observe that most of the diseases of the blood-forming tissues are associated with intermittent pyrexia, that they occur, for the most part, more frequently in men, and that they are subject to periodic remissions. In these three respects they resemble paralytic dementia. In simple fracture of a bone the marrow becomes involved; similarly in neoplastic disease. In fracture the condition is strictly localized, and in neoplasm it remains so for a time. As there is no evidence that any substance is produced which gives rise to pyrexia in either of these conditions, it is fair to assume that the pyrexia is associated with a localized process involving the reticulo-endothelium of the marrow. The anæmia secondary to repeated hæmorrhages is

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accompanied by pyrexial attacks and increased activity of the marrow.

The conditions which produce an abnormally low temperature are nearly all the antithesis of those which cause pyrexia, and the majority are associated with retardation of bodily metabolism, whether from deficient intake, as in starvation, or from the general exhaustion consequent upon long-standing diseases such as chronic nephritis, malignant disease or chronic pulmonary and cardiac disorders. After acute infections the temperature may remain subnormal for many weeks. At the same time the blood may show corresponding changes. Whereas during the fever neutrophilia occurred, the blood may now exhibit a post-infective eosinophilia or lymphocytosis. Fever may, on the other hand, give rise to neutropenia, as in typhoid fever or after several paroxysms of malaria. Likewise pyrexia occurs sometimes in aplastic anæmia, in which there are few signs of myeloid activity.

The close relationship which exists between the production of pyrexia and functional disturbances of the hæmatopoietic tissues suggests the possibility of a definite pyretogenic function being assignable to the reticulo-endothelial system. There is, however, no reason to suppose that the two functions of pyretogenesis and hæmatopoiesis are inseparable. Pyrexia forms only part of the somatic reaction instituted by the reticulo-endothelial system, including the spleen, in order to establish resistance and immunity to infection.

Results of the Investigations.

1. *Untreated Paralytic Dementia.*

Lymphatic tissues.—A moderate overgrowth of the fibrous element in the trabeculæ occurred which was not confined to any particular set of glands. No other points of interest were observed.

Bone-marrow.—To the naked eye the marrow in the ribs was bright red. Microscopically the whole was obviously engorged with blood. In some specimens the trabeculæ were clearly thickened through increase in the amount of reticular fibres. In the detached cells, however, a more notable variation from the normal occurred. There was a marked scarcity of neutrophilic leucocytes. Their precursors, the myelocytes, were also less in evidence than is usual. The normoblasts and red cells in the blood-channels composed the vast majority of the cells present, and they possessed no appreciable abnormalities.

It is striking that the changes found in the bone-marrow were absent in eight non-paretic syphilitic subjects, in all of whom the Wassermann reaction had been positive in the blood. In two the

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cerebro-spinal fluid gave negative results to the Wassermann and colloidal gold reactions and there was no excess of cells. In the remainder it was not examined.

The Blood.

Red cells.—In the early stages of the disease numerical and morphological changes were not conspicuous. In the advanced stages, however, the numbers fell as low as four million, the colour index being about 0·8. The size and shape of the cells showed no appreciable change.

Leucocytes.—During the first and early second stages of paralytic dementia the total and differential counts remained within normal limits, with a Schilling index of about 5%. The Schilling index, to which reference will frequently be made in the following pages, is the number of immature neutrophilic leucocytes, or meta-myelocytes, calculated as a percentage of the total number of leucocytes. A metamyelocyte is taken to be a cell the nucleus of which is indented but shows no true lobulation.

When weakness and wasting became apparent the Schilling index rose to 19 to 20%. Finally the total number of leucocytes fell to 4000. The leucopenia was almost entirely accounted for by a reduction in the number of neutrophilic cells.

During the pyrexial attacks which are characteristic of the middle and later stages, a slight absolute increase in the number of lymphocytes occurred. In some pyrexial attacks, more especially in the later stages and probably due to intercurrent infection, a slight neutrophilia was noted, bringing the total leucocyte-count from 4,000 up to 5,000 or 6,000, the differential count being thereby restored within normal limits.

2. *The Blood in Relapsing Fever.*

(*a*) *In otherwise Healthy Subjects.*

The number of red cells and the amount of hæmoglobin are slightly reduced throughout the disease (13). The febrile paroxysms are accompanied by a moderate neutrophilia which becomes well marked before the crises preceding the termination of the paroxysms (13).

(*b*) *Associated with Paralytic Dementia.*

The red cells.—The usual number were about five million in both sexes. The colour index was 0·8. The size of the corpuscles varied within a wider range than normal, but no abnormalities with regard to shape were observed. It was unusual to find a normoblast,

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and only an occasional cell was seen which showed reticulation in films stained with cresyl blue. Immature forms, therefore, were rare.

The leucocytes.—There were well-marked changes which varied in intensity according to the stage to which the paralytic dementia had advanced. The total number, in favourable cases, followed closely the course of the temperature curve, rising to 9,000 or 10,000 at the beginning of a paroxysm and reaching 13,000 at its height. During the afebrile intervals the numbers fell to 5,000. Neutrophilia was almost entirely responsible for the increased number of leucocytes. After three or four paroxysms the leucocytosis tended to become less marked, especially in the more advanced cases of paralytic dementia.

Neutrophilic leucocytes.—It has already been observed that the Schilling index was normal during the earlier stages in untreated cases. It rose, however, to 10% during the first paroxysm of relapsing fever, becoming higher during later paroxysms. In favourable cases the index seldom rose above 30%. In advanced cases, and in those which declined under treatment, the index was high from the start, and stood at 40% to 60% during the second and subsequent relapses of fever. In the afebrile intervals, in all cases, the index stood above the normal 5%. It returned to normal, in mild cases and those which improved under treatment, within six to nine months of the termination of the relapsing fever.

Myelocytes.—Neutrophilic myelocytes were found in smears taken from 16 subjects, but in no case did they exceed 2%. Their presence was independent of the level of the Schilling index.

Eosinophilic leucocytes.—It was rare to find more than 0·5% of these cells during either the paroxysms or the afebrile intervals. They reappeared, however, to the extent of 4% or 5% after the termination of the fever. No morphological changes of interest were observed.

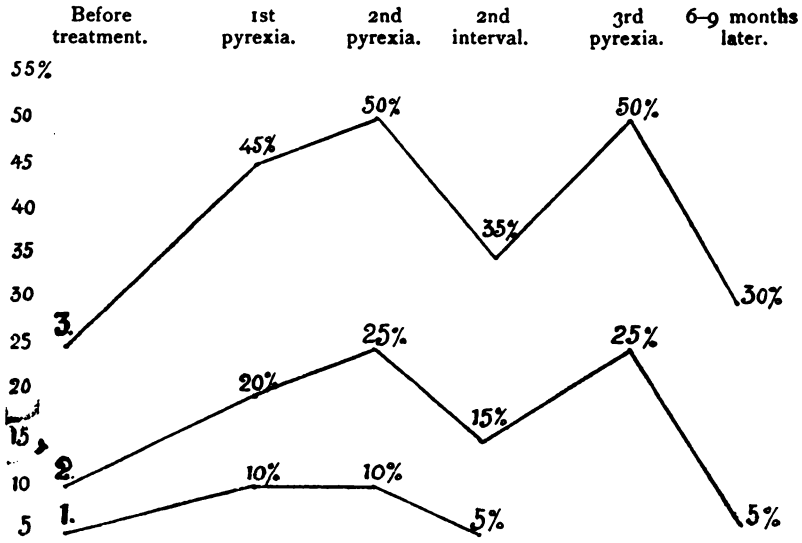
Basophilic leucocytes.—During the whole course of the relapsing fever basophilic cells were scanty.

Monocytes.—The large hyaline leucocytes of the blood and the so-called transitional leucocytes were all classed as monocytes. At the onset of the first febrile period the numbers rose to 10%, falling to 6% during the afebrile intervals. After three or more relapses they seldom exceeded 8%. Rather more than half the number of cells contained neutrophilic granules in the cytoplasm. The nuclei varied greatly in outline, some being deeply notched, while others were merely flattened at one point. An interesting fact was brought to light when smears were stained by means of Pappenheim's method. Many of the granular monocytes exhibited

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lymphoid characteristics in regard to their nuclei (14). The question at once arose of the existence of two varieties of these cells, one being of myeloid origin and the other of lymphoid (15).

Lymphocytes.—The number was relatively diminished, but it actually remained within normal limits. Large forms constituted nearly half the total number of lymphocytes, some of which were with difficulty distinguished from the smaller monocytes, especially those lymphocytes which possessed a flattened or slightly indented nucleus. The lymphocytic nuclei, however, assumed a slightly



Schilling Index in Relapsing Fever: 1. Acute mania in a non-paretic subject. 2. A case of early paresis improved by treatment. 3. An advanced case of paresis which deteriorated under treatment.

deeper shade of blue with Leishman's stain. Moreover, when stained by Pappenheim's method, the nuclear chromatin in similar cells presented the lymphoid characteristics, and they were therefore classified as lymphocytes.

Sagel (16) found somewhat similar results in his examinations of the blood, but he considered that a post-infective lymphocytosis was common. In the cases under consideration this lymphocytosis was relative only.

(*c*) *Six to Nine Months Later.*

The results varied according to the stage to which the paralytic dementia had progressed before the treatment and the degree of leucocytic reaction obtained during treatment. In mild cases, or

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those which produced a good reaction, the total leucocyte count was found to be within normal limits, with the Schilling index restored. In more severe cases, however, or those which either gave a poor leucocytic reaction or became worse during the induced fever, the total leucocyte count amounted to only 4,000 with 40% of lymphocytes, as compared with 5,500 leucocytes and 30% of lymphocytes in the same cases before treatment. The proportion of monocytes had returned within normal limits.

In no case did the induction of relapsing fever produce any change in the intensity of the Wassermann reaction in either the blood or the cerebro-spinal fluid at this stage of the investigations.

Some typical blood-counts were included in an earlier communication (23).

3. *The Blood in Malaria.*

(*a*) *In otherwise Healthy Subjects.*

In benign tertian malaria a mild leucocytosis is said to occur during the paroxysms (17), associated with a slight rise in the Schilling index. The leucocytosis is due to an increase in the number of neutrophilic cells, the subsequent withdrawal of which leads to leucopenia. During the febrile periods the monocytes are more than normally plentiful.

(*b*) *Associated with Paralytic Dementia.*

Published accounts of the blood-changes differ slightly from one another. Alberto (18) and Hattori (11) found that myelocytes occurred up to the extent of 15% in the early febrile attacks, disappearing completely after about the fifth paroxysm, by which time the blood picture approximated to the normal. They did not mention the Arneth count or Schilling index. During the earlier febrile periods plasma-cells were present in the blood (11). Saunders (8), as already mentioned, found that a " shift to the left " occurred in the Arneth count in untreated cases of paralytic dementia, which was entirely corrected six to twelve months after malarial treatment.

The Relationship between Reticulo-Endothelial Disorders and the Pathogenesis of Paralytic Dementia.

The relationship between syphilis and blood diseases is obscure, but certain facts are known. For instance, syphilis may produce a condition clinically resembling pernicious anæmia. Kyrle (20) found that syphilis caused, in some cases, a slight leucocytosis which was not influenced by treatment, and in others a more marked leucocytosis which was reduced to normal during treatment. Zanca (21) describes hypoplasia of the marrow in association with

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congenital syphilis. It is well known that the more severe syphilitic changes in the blood are confined almost entirely to the third stage. Hoff (22) stresses the importance of blood changes in syphilis, and states that the Wassermann reaction is unreliable in obviously syphilitic subjects suffering from pernicious anæmia, and that it is frequently negative.

The lesions of the central nervous system in paralytic dementia consist of—

1. Meningo-vascular lesions and
2. Neuronic degeneration.

The meningo-vascular lesions resemble those of meningo-vascular syphilis which is not a part of paralytic dementia, except that their distribution is more widespread and that they are more productive of neuroglial proliferation. There is a conflict of opinion as to whether the neuronic changes are primary or secondary, but the majority favour the latter view. It is highly probable, however, that some other pathogenic factor is at work which determines whether a given syphilitic subject will develop paralytic dementia.

The association of syphilis with disorders of the reticulo-endothelial system has already been mentioned, and evidence has been produced to show that the hæmatopoietic functions, especially those of the bone-marrow, are depressed in paralytic dementia in proportion to the stage to which the disease has progressed, as shown by the diminution in the leucocyte reserve in the bone-marrow and the output of immature neutrophilic cells when leucopoiesis is stimulated. This may also account for the readiness with which paretic patients develop bed-sores.

The Rationale of Pyretotherapy.

It has been recorded above that the leucopoietic function of the reticulo-endothelial system is depressed, and that syphilis, apart from paralytic dementia, may produce a condition which bears a close clinical resemblance to pernicious anæmia. In paralytic dementia the interference with the leucopoietic function, which has its analogy in the pathogenesis of pernicious anæmia, suggests that the former may be due to syphilitic affection of the reticulo-endothelial system—a process which is obviously combined with meningo-vascular syphilis. Further, remissions are a characteristic of the clinical progress of both diseases, and both occur more frequently in men. It appears that the spectre of a damaged reticulo-endothelium looms up constantly in the pathogenesis of paralytic dementia. It follows, therefore, that the line of attack in treatment should be directed towards stimulating the defensive

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reactions of this tissue, and the greatest success in this direction has been won by the induction of infective fevers, especially that of malaria.

It is a matter of common knowledge that, in some way, induced fever stirs up resistance to the luetic infection, shown by clinical improvement and by reduction in the intensity, after twelve months, of the Wassermann reaction in the cerebro-spinal fluid. The cytological changes in the blood during treatment form another indication of this reaction. Yet the records will be searched in vain for any expression of the view that depression of the reticulo-endothelium is a factor in the pathogenesis of paralytic dementia, or that the benefits of pyretotherapy are conferred through rectification of this fault. Attention has, so far, been fixed either upon the effects of the raised temperature itself, or upon the possibility that the somatic reaction to the therapeutic agent may be, in an indefinite way, coincidentally lethal to the syphilitic virus. The intensification of the Wassermann reaction which is said to occur in rare cases during malarial treatment has hitherto been a pathological enigma. It should be regarded as a sign that the tissue concerned with the production of resistance and immunity, namely, the reticulo-endothelial system, is showing increased activity, since the Wassermann reaction may be looked upon as a phenomenon of resistance to infection.

Therapeutic Problems.

(*a*) *Choice of Fever.*

Published work shows that malaria has undoubtedly afforded the most satisfactory results from a clinical point of view. Now malaria exerts a transient stimulatory effect upon the leucopoietic functions, which is followed by an inhibitory action shown by the subsequent leucopenia. At the same time active phagocytosis is stimulated in the brain, and plasma-cells appear in the peripheral blood. These cells were not observed in the blood of patients treated with relapsing fever, and their absence denotes a less intense action upon the reticulo-endothelial system on the part of the therapeutic agent. It must be admitted, however, that no opportunity was found to investigate the brains of patients treated with relapsing fever, because no member of the series died before the investigations were closed.

(*b*) *Choice of Patient.*

Of the cases treated with relapsing fever, it was found that some continued to decline under treatment, or even to show acceleration

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of their progress. In these there was a poor leucocytic response, with a high Schilling index. Others, on the contrary, showed improvement. Their leucocytic reaction was good and the Schilling index was restored to normal limits. It would seem reasonable, therefore, when the application of malarial therapy is contemplated, to test the power of leucogenic response by some mild means, such as the injection of sodium nucleinate or peptone, before resorting to the more drastic malarial treatment, rejecting those who give a poor response, and accepting only those in whom the reticulo-endothelium is in a good condition to respond without the risk of over-stimulation of an already exhausted tissue. We thus have at our disposal a method of estimating, to some extent, the probable effect of pyretotherapy in any given case. In practice this would mean that pyretotherapy would be available, not only for early and mild cases and a few of the more advanced, but also in a way which will be referred to later.

(*c*) *After-Treatment.*

It is the usual custom in this country and on the Continent to keep the patients under observation as long as possible after a course of malarial treatment, and even to give a second course if this is indicated. In view of the obvious importance of the hæmato-poietic functions, any measure known to stimulate them should be applied to the patient who has undergone malarial treatment—for instance, residence for a time at a high altitude, which is known to produce an erythropoiesis. It is possible that stimulation of one function of the reticulo-endothelium, namely, erythropoiesis, might result in increased activity of such a closely allied function as leucopoiesis, since both types of cell are derived from the bone-marrow, the only difference being that the former is intravascular in origin while the latter is extravascular.

Since malarial therapy can convert a case of paralytic dementia into one of meningo-vascular syphilis, it follows that a subsequent course of arsenicals is indicated.

(*d*) *Prophylaxis.*

There are, in the experience of every psychiatrist, cases of paralytic dementia who have a clear history of having been diagnosed as syphilitic only after their blood had been found to be positive to the Wassermann reaction in the course of investigation on account of some other illness, and in whom there have been few, if any, manifest syphilitic lesions. This class is one in which the administration of the usual anti-syphilitic remedies is notoriously

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unsatisfactory. In view of the findings described in this thesis it may be concluded that malaria should, in these cases, be tried as a prophylactic measure, followed by the usual anti-syphilitic treatment.

Summary.

In the series of cases under consideration it was found that changes occurred in the bone-marrow and blood in paralytic dementia, which showed that the leucopoietic functions were impaired and that the leucocyte reserve was diminished. In untreated cases there was a definite leucopenia.

When leucocytosis was stimulated the intensity of the neutrophilic reaction varied inversely with the stage to which the paralytic dementia had advanced.

Under the same conditions the Schilling index rose in direct proportion to the stage of the disease. The rise was most marked in those cases whose decline was accelerated by pyretotherapy, and least marked in those who were benefited.

Six to nine months after treatment by the induction of relapsing fever the Schilling index, in favourable cases, was restored to normal limits after having been at a higher level before treatment. This is in accord with the experience of other writers with regard to the effects of malarial treatment.

The better the condition of the patient after treatment, the nearer did the differential leucocyte count and Schilling index approach the normal, and the converse was equally true.

The changes described above are referable to affection of the reticulo-endothelial system. An analogy has been drawn between paralytic dementia and pernicious anæmia. That syphilis may attack this system is evident from the fact that it may produce a condition clinically resembling pernicious anæmia. Yet this need not always be the case, for the writer detected no appreciable rise in the Schilling index when neutrophilia was artificially induced in syphilitic subjects in whom paralytic dementia was not evident, nor were any signs of impairment of the leucopoietic function detected at autopsy.

It would appear, therefore, that involvement of the reticulo-endothelium by the syphilitic virus constitutes one of the factors which determine whether a given syphilitic subject will develop paralytic dementia. Strength is lent to this hypothesis when it is remembered that the type of subject who develops paralytic dementia is one in whom a scanty history of earlier syphilitic lesions indicates absence of reaction against the infecting organism.

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Since involvement of the reticulo-endothelial system is a characteristic of paralytic dementia, it follows that therapeutic measures should take this into account.

In general, pyrexia is associated with a leucocytic reaction resulting in numerical changes in the leucocyte-content of the blood—that is to say, the reticulo-endothelial system takes part in the genesis and control of pyrexia.

Treatment by means of leucogenic infections resulted at first in emphasizing the changes which paralytic dementia produces in the leucopoietic functions. The later effects consisted in the correction of these changes in the cases which derived benefit from the treatment, and in the reverse in those which were unimproved. In other words, pyretotherapy stimulates the resistive function of the reticulo-endothelial system at a time when this function is flagging under the influence of a chronic infection, namely, syphilis.

From the pathological point of view, some writers have found that malaria can convert paralytic dementia into a condition of meningo-vascular syphilis which may even assume a diffuse gummatous nature. Others describe increased reaction on the part of the reticulo-endothelium of the cerebral blood-vessels during the malarial attack, with subsequent restoration of the cortex. It is significant that a therapeutic measure which relieves the depression of the leucopoietic function should either stimulate the cerebral reticulo-endothelium and then restore it nearly to normal, with consequent clinical improvement, or else convert a paretic condition into one of meningo-vascular syphilis.

From the therapeutic point of view the following considerations arise:

1. Malarial therapy should be reserved for those cases in which a satisfactory leucocytic reaction has been obtained by means of a preliminary test with a mild leucogenic agent.

2. In view of the importance of the reticulo-endothelial disturbance, patients who have derived benefit from malarial treatment should reside for a time at a high altitude in order to stimulate erythropoiesis, in the hope that the closely allied function of leucopoiesis will benefit.

3. Prophylactic malarial treatment should be advised for all patients who are known to suffer from syphilis in whom few, if any, secondary or tertiary lesions have been observed.

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