NOTES ON THE SIGNIFICANCE OF FEVER IN SYphilis WITH A REFERENCE TO HYPOpyrexia.

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If, as should be done, the temperature is taken and recorded regularly in cases of syphilis at all stages of the disease and of the treatment, a more or less raised temperature can often be demonstrated. It is possible that one patient in every six will present some thermal upset. Thermal upset may occur:

1. With fever as one of the presenting signs and symptoms in some stage.
2. As hypopyrexia.
3. With fever as an indication of the reactivation of syphilis by various agents, either physical or chemical, i.e. "biotropism".
4. With fever from intercurrent disease which either arises de novo or is activated by the syphilis and/or its treatment.
5. With fever as a manifestation of intoxication by, or intolerance to, the drug used.

SYPHILITIC FEVER may occur (a) with eruption, i.e. "eruptive fever" and (b) without eruption or syphilitic fever properly so-called, or "essential fever".

This fever was thought to be very much more frequent in women than in men, especially in young women suffering from secondary syphilis; since this form of syphilis was regarded rather as the concomitant of young women.

However, experience in Abyssinia, the Somalias and East Africa, in treating more than 20,000 native male patients suffering from various types of V.D. has shown that secondary syphilis is very common amongst such natives and that raised temperature from different causes is far from rare amongst them, pointing to the importance of a correct interpretation of these pyrexias.

"Eruptive Fever".—By this is understood the fever which may precede and sometimes accompanies the eruptions or mucocutaneous manifestations of syphilis, especially in the secondary stage and particularly with roseola and the florid generalized papular eruptions.

There is a prodromal fever of 100° to 103° F. (cf. other infectious diseases), lasting four or five days, and falling almost to normal as the rash becomes marked.

This fever is at times associated with more serious manifestations such as iritis, periostitis, syphilitic pseudo rheumatism, adenopathy, etc.

"Essential Fever".—This is syphilitic fever properly so-called and used to be considered almost exclusive to females who were in their first months of the secondary stage of syphilis.

There are three types of this fever:

(i) Intermittent, which is the most usual and is apt to be confused with malaria, but shows daily exacerbations as opposed to the three or four day periodicity with apyrexial intervals of malaria.

There are feverish attacks of 101° to 102.4° F. with general malaise, shivering rather than rigors, and flushing and sweating usually in the evenings. Splenic enlargement is unusual or only slight and blood parasites are absent. Anti-syphilitic treatment causes cessation of the attacks.

There may be confusion with tuberculosis though, in the latter, the night sweats are more profuse.

(ii) Continuous fever may be moderate around 100.4° F. or intense around 102° to 104° F.
(rare), and may be accompanied by various symptoms including generalized muscle pains and gastric disturbance, suggesting typhoid and paratyphoid fevers. These latter are not uncommon in syphilitics in the secondary stage but, in a patient without marked gastric upset, in good general condition with a clean moist tongue suffering from this type of fever, syphilis must be considered.

This continuous fever rarely persists longer than six or seven days, but sometimes a true syphilitic fever lasts two or three weeks, or shows 2 or 3 plateaux each lasting about seven days. If there is asthenia, stupor, torpor or somnolence accompanying the fever, a syphilitic typhoid state might be mistaken for true typhoid.

These febrile forms of syphilis cannot, and must not, be diagnosed solely on clinical grounds. Laboratory aid, including blood culture and agglutination tests, is essential.

(iii) Irregular fever is a mixture of all types. First irregular, then continuous, then repeating an irregular mixture of the two types in a completely capricious manner, the beginning, the rise and the fall being altogether unpredictable. This irregular fever is not uncommon.

Fever in Primary Syphilis.—Milian has described a small series of 21 patients with primary syphilis but without inflammatory adenopathy, skin manifestations or other organic affection capable of producing fever, in whom noteworthy febrile reaction was remarked in four cases.

There was slight rise in temperature to 100°F; no sweats and no rigors; apparently commoner in females; occurred a few days after the chancre appeared and particularly with multiple chancres, i.e. severe infection.

Even following a simple injection of mercury, these feverish primary syphilitics are liable to produce marked Herxheimers Reaction with a considerable further rise in temperature.

Fever in Secondary Syphilis.—This fever is recorded as a plateau around 100°F and rarely more than 101°F. It may last for days or weeks if the appropriate drug is not given.

This fever may be launched, as it were, by the beginning of the exhibition of treatment and is, in these cases, the indication of the development of an important spirochetal centre or focus which is usually visceral.

Fever of Early Malignant Syphilis.—This fever oscillates between 100°F and 103°F, and may last a month. Usually there are morning remissions. The fever is frequently entirely uninfluenced by mercury but reacts to arsenobenzol and, in a patient riddled with ulcers, it might lead to the suspicion of secondary infection with other organisms were it not for the efficacy of treatment with arsenobenzol.

Fever in Tertiary Syphilis.—This occurs as in secondary syphilis, and there may be (i) continuous fever in the region of 102°F for weeks, without noteworthy symptoms or with only discrete signs of syphilis. This type of fever without other flagrant cause is almost characteristic of the disease. (ii) Fever with gross oscillations when there is almost hyperpyrexia of 103°F to 105°F with enormous irregularities. This condition is often thought to be tuberculosis or due to infection with B. coli. Both liver and spleen may be enlarged causing suspicion of suppurating hydatid cyst or of liver abscess, but the excellent general condition of the patient is usually a revealing pointer, and anti-syphilitic treatment in these cases has generally a rapid and sovereign effect.

Prolonged fever after accouchement and without puerperal explanation has been observed and described in syphilitics and has cleared up with the exhibition of anti-syphilitic treatment. False diagnoses and dangerous surgical intervention may be avoided by recalling this type of fever.

Hypopyrexia in Syphilis may occur in :

(i) Acquired Syphilis, but it is rare and only occurs in the secondary stage.

It is probably due to the associated anemia, but there may be some syphilitic alteration in the Central Nervous System (bulb) or some vago-sympathetic affection or even some action on the thyroid which could account for the disturbance.

Whatever the cause, the hypopyrexia disappears with the anemia under anti-syphilitic treatment.
(ii) Hereditary Syphilis in Nurslings.—In these cases, hypopyrexia is quite common (at around 96° F.) both in those with florid skin lesions as well as in those born with no revealing external signs or, in fact, in those born with every appearance of health.

Under the influence of specific treatment the hypopyrexia disappears, progressively and parallel with the intensity and duration of treatment, and there appears to be no relation between the weight and the temperature charts in these cases.

Many of them are resistant to treatment, especially when there are marked visceral changes, particularly in the liver. They are usually very heavily infected and much patience is required.

The liver appears to play a very important part in thermal regulation.

Fever as an Indication of the Reactivation of Syphilis of the Fever of Therapeutic Conflict in Syphilis.

"Therapeutic conflicts" of drug versus germ are accompanied by exacerbations of fever up to 102° to 104° F., the rise occurring soon after injection of the drug, but the temperature falling almost to normal within twenty-four hours.

This fever is a definite indication of the conflict in certain cases, where biotropism obtains with regard to the treponema, but where appreciable (clinically helpful) skin or visceral reactions are not provoked.

Therapeutic conflict does not always happen. Many cases of syphilis are treated without the least elevation of temperature. These are cases where the disease is quietly overcome by the medication and they have an excellent prognosis.

The feverish reactions to the battle between the disease and the drug are accompanied by shivering, sweats and general malaise starting just like an attack of malaria. They do not show any of the phenomena usual with arsenical poisoning.

The progressive disappearance of the fever on continuing medication seems to prove that these attacks are reactional and not toxic.

These pyrexial reactivations occur, not only at the beginning of the course of treatment, but even during the course and at the end of it in those cases of syphilis which are partially or totally resistant to medication with arsenic. They must be considered in any explanation of such phenomena as inter-therapeutic jaundice, and in post-therapeutic jaundice and neuro-relapses, etc., because the feverish reactions as well as the skin and mucous membrane reactivations show the possibility and the reality of the lighting up of visceral lesions under the influence of treatment.

By their persistence during the course of treatment these feverish attacks show that the living virus persists in the body. It is necessary to continue treatment, the cessation of which might prove dangerous.

When the pyrexial attacks occur during treatment with arsenobenzol, and disappear with the administration of mercury or bismuth, it is shown that, in certain cases, mercury or bismuth have a superior curative action to arsenic.

Stimulation of the parasite rather than a weakening of the body is suggested as an explanation of these feverish attacks because (i) they disappear when the dose is increased and the greater the augmentation of the dose the more quickly does the temperature fall and, (ii) the administration of the drug often provokes not only a rise in temperature on the day of injection, but sometimes a continuous fever lasting days or even weeks and with all the characters of the syphilitic fever described above: a fever typical of that associated with secondary syphilis—staying around 100°-101° F.—and disappearing with the administration of a different anti-syphilitic drug, i.e. mercury or bismuth.

Charts of pyrexia accompanying therapeutic conflict often show clearly the intensity of feverish reaction following injection, and then the extinction of the feverish reaction in proportion as medication is continued, e.g. —

(a) Case of secondary syphilis: Thermal reaction to 104° F. after the first injection of 0·45 gramme NAB; normal the day following. The only symptoms accompanying the fever were those like an attack of malaria, and without any real phenomena of intolerance

96°
like vomiting and diarrhoea. A second dose of 0.45 gramme NAB was injected four days later, the dose not being increased in order to make sure that intolerance did not obtain. This second dose produced a temperature of 100.4° F., which fell to normal the day following. The third dose was of 0.6 gramme given five days later and produced fever of 100° F.; fourth dose of 0.6 gramme given after another five days gave fever of 100° F.; fifth dose, six days later of 0.75 gramme gave fever of 100.6° F.; repetition of this dose after a further six days produced no fever, and the course was completed to a total of 5.65 grammes in three further injections at six-day intervals without incident.

(b) Another case: First injection of 0.45 gramme and second injection four days later of 0.6 gramme gave no fever. Third injection of 0.6 gramme after a further five days produced fever of 104.6° F. Did this signify intoxication by or intolerance to the drug? The only symptoms were those described above, as with an attack of malaria, and suggesting microbial resistance rather than intoxication. The dose was increased to 0.75 gramme after a further six days and provoked fever to 103.8° F. as compared with the previous 104.6° F. Continuing the dose of 0.75 gramme at the next injection, the fever was 101.8° F. This reduction seemed encouraging and the treatment was continued with doses of 0.75 gramme to the end of the course with rapid lessening of feverish reaction.

It is probable that a quicker fall to normal would have occurred if doses of 0.9 gramme had been used.

(c) A third case: Four injections of 0.45 gramme NAB at five-day intervals each produced general and thermal reactions once reaching 105.4° F. with the fever persisting for two days after the last injection. Mercury salicylate was then given intramuscularly every other day for 3 doses and then again for 4 doses at three-day intervals. No fever occurred with the mercury, and it was possible to resume and continue treatment with NAB at doses of 0.6 gramme and then 0.75 gramme with no further reactions.

The fact that the mercury did not produce fever and that later doses of NAB could be given without reaction helped to show that the treponema was the cause of the initial fevers and not intoxication.

Activation of Syphilis. Biotropism and Syphilis.

Physical Agents.—These can light up latent syphilis. X-rays do so at times, and produce an acute and erythematous form of lesion which develops with extreme rapidity and suggests that the vitality of the spirochète is stimulated and that it becomes excessively virulent. Radium may have the same effect.

Cold is said to have a stimulant effect on microbial germs living in a saprophytic state in the body. It may bring about syphilitic nephritis, of which the syphilitic element may be missed. Equally it may provoke paraplegias in the secondary stage of syphilis. Cold, particularly damp cold, change of climate and the imminence of storms frequently excite the pains of tabetics.

Humidity and humid climates will provoke pain, swelling and deformity of fingers in a patient with chronic syphilitic rheumatism as early as the fourth or fifth day in such a climate. Mercury injections will make him comfortable.

Chemical Agents.—Despite their curative properties, drugs used in the treatment of syphilis can, under certain conditions, provoke activation of the disease (cf. provocative dose of NAB prior to Kahn test).

Syphilitic lesions of skin and mucous membranes are frequently increased, enlarged and multiplied by the initiation of treatment. These focal reactions are what are known as Herxheimers Reaction, and seem only to be explained by biotropism.

Similar reactions can and do occur in the viscera. Hepatic or renal symptoms may increase instead of diminish with treatment, and they are then frequently attributed not to the disease itself but to intoxication by the drug used. Intoxication can, of course, occur but the time factor, the chronological connection between the administration of the drug and the appearance of morbid phenomena, should be noted as a differentiating agent.
It is continually necessary to remind oneself that what is apparent on the skin as a result of syphilis, may have comparable lesions in the viscera.

This is particularly the case with the liver when, for example during treatment, jaundice appears which has all the characters of jaundice of secondary syphilis, i.e. jaundice of retention: liver and spleen enlarged; tongue moist and no fever. Diagnosis is by no means easy but, if there are no other signs of arsenical intoxication, one can be reasonably certain that the jaundice is infectious, i.e. syphilitic and not toxic.

The great difficulty in many cases, especially in the African with his already otherwise affected liver, is to decide whether the biotropism is direct, i.e. towards the treponema, or indirect towards some other latent infection of the body, e.g. malaria.

Nerve involvement is also quite common as a biotropic manifestation of syphilis. The facial and auditory nerves swell in the aqueduct of Fallopius and are there compressed. For the cochlear branch of the auditory nerve, the reaction of activation is shown by buzzing in the ears and deafness. Reactivations in the vestibular branch may be shown by vertigo and vomiting.

Thus there may be almost an appearance of cerebral accident, with sudden blindness, or deafness, or inability to speak. A number of such cases were seen in Abyssinia, and all reacted well to bismuth therapy.

The fulminating pains of tabes may be evoked under the influence of treatment, but diminish with the injection of larger doses of drug at shorter intervals.

These reactivations are usually accompanied by feverish reactions more or less violent. Actually, since one does not see inside the body, the fever may be the only appreciable sign of reactivation. In other words, there may be no recognized visceral localization, but only a feverish reaction with general malaise, muscular pains and shivering.

It is mostly with the small dose of drug that the danger of therapeutic conflict is established; meaning that these therapeutic activations are most frequently observed when treatment has been insufficient as to dose and duration. They may also occur when the spirochete has been particularly resistant to the drug used, and they can then occur with medium or even large doses, especially of arsenobenzol which is pre-eminently the most activating of all the anti-syphilitic drugs.

Above all, it must not be thought that feverish reactions will occur in every case, nor indeed after every injection. Even if temperatures are taken with care, it is not more than one in six patients who presents febrile reactions; providing always that due regard is paid to the quality and administration of the drug and to the previous history and the preparation of the patient.

Infectious Diseases.—These can light up old syphilis and produce syphilitic lesions in patients whose syphilis was thought to have been extinguished.

Such diseases are pneumonia, typhoid, "rheumatism," herpes and scarlet fever. When rare complications such as gangrene of toes or arteritis obliterans arise during any of the infectious diseases, the presence of syphilis should always be suspected.

Similarly, syphilis may activate latent pyrexias as malaria.

Intercurrent Disease.—Accidentally simultaneous diseases need no elaboration in these notes.

Fever as a Manifestation of Intoxication by the Drug.

The dosage, administration and particularly the quality of the drugs (arsenicals) used have been discussed in a previous memorandum.

The following are a few points in the comparison between intoxication and intolerance which may prove helpful.

Intoxication is produced by an agent which is poisonous.
The noxious dose is more or less identical for everybody.
The effects increase with each addition of the drug, i.e. the effects are proportionate to
the dose.  
The effects are logically connected with the cause, different drugs producing different
reactions.
The agent (drug) plays the greater part, the soil (patient) being accessory.

Intolerance.—Here the noxious agent is a reactogen and may be an inoffensive body like
albumin, or even a physical agent.
The noxious dose varies with the individual.
There may be no noxious effect from large doses.
The intolerance may seem paradoxical, depending on the individual.
Identical reactions occur with different causes and are either (a) general: neuro-vegetative
or vascular, or (b) local: inflammatory.
The soil (patient) plays the greater part, the agent (drug) being accessory.'

In the charts of fever with intoxication, which are rare in comparison with those described
above, the thermal reaction appears late after the injections, and increases in a progressive
manner until the appearance of toxic signs and symptoms, for example vesiculo-oedematous
erthrodermia.

There is always vomiting and diarrhoea, the body seeking to rid itself of the poison by
every means.

Conclusion.

Pyrexial attacks in syphilis have been described suggesting:
(i) The possibility of fever being the presenting sign of syphilis.
(ii) The danger of insufficient dosage and the necessity for not losing time by using feeble
doses of arsenicals in the treatment of syphilis.
(iii) The importance of recognizing thermal reactions during the treatment of syphilis
as an index to the resistance of the treponema, and as an indication of the necessity for
either (a) increasing the dosage of arsenical or, more frequently, (b) changing the drug used,
i.e. from arsenobenzol to mercury.
(iv) The advisability, in syphilitics who have had no treatment for some time, of preceding
the exhibition of a course of arsenobenzol by the administration of mercury or bismuth for
a sufficient time.
(v) The advisability of preceding the arsenobenzol by several spaced injections of bismuth
in any syphilitic with florid skin manifestations.
(vi) Recognition of the fact that if sufficient mercury or bismuth is injected over an
adequate period, the subsequent administration of arsenobenzol is unlikely to produce any
activation of lesions or any febrile reactions.  ...  To the greater physical comfort of the
patient as well as to the greater mental comfort of his medical adviser.

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