THE ETIOLOGY AND HAEMATOLOGY OF OBSCURE FEVER

A Contribution to the Diagnosis of the Causes of "Pyrexia of Undetermined Origin"

T H E S I S

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THE PLAN AND PURPOSE OF THIS THESIS

The aim of this thesis is to contribute to the solution of an ever recurring problem in clinical medicine, more especially in general practice, namely, the diagnosis of the causes of obscure fever.

From a survey of the pyrexial diseases listed in the standard text books of medicine together with a study of the literature, it has been possible to collect 51 disease entities which are potentially responsible for the clinical presentation with prolonged or recurring fever without localizing symptoms or clinical signs. These diseases have been classified on an anatomico-etiological basis. Evidence is adduced to show that these affections may present with pyrexia as their dominant or only clinical manifestation.

The next step was to find a starting point for breaking up this large field of possibilities into a series of smaller groups for the purpose of differential diagnosis. To this end it was decided to examine the potentialities of the routine blood count as a simple, universally applicable, laboratory procedure. A detailed study was therefore undertaken of the peripheral blood responses of the 51 diseases with which we are concerned. The result of this study has shown that the trend of the leucocytic pattern as revealed by serial haemography constitutes an eminently satisfactory groundwork for a

haematological grouping of the obscure fevers. It is desired to emphasize that the peripheral blood responses of the diseases presenting with obscure fever are not static but dynamic requiring serial repetition of the blood count to elucidate their characteristic blood patterns.

Finally, a case record is submitted to demonstrate the value of the haematological approach in the etiological diagnosis of obscure fever.

C O N T E N T S

P A R T I

THE CAUSES OF OBSCURE FEVER

It will be generally agreed that the most important single factor in the diagnosis of the cause of an obscure fever is a high sense of alertness to the possibilities to be considered. It is necessary therefore, first of all, to gather together all those affections which possess, as their common denominator the clinical presentation with fever. Before such a collection can be made, however, two questions have to be answered. 1. What is fever? and 2. When shall a febrile illness which continues to present with pyrexia as its major clinical manifestation be termed an "obscure fever?"

In answer to the first query it is well to remember that the normal temperature is no more than an <u>average</u> figure derived from the readings of large numbers of apparently healthy persons. Samson Wright[95] gives the following normal values: "Mouth 96.7° to 99°F; rectum 97.2° to 99.5°F ... The temperature is highest in the evening and lowest in the early hours of the morning. The time of the maximum temperature is usually between 5 and 8 p.m." Most clinicians will agree that a buccal temperature of 99°F and a rectal of 99.5°F may be taken as the highest normal, and that figures above these limits constitute pyrexia.

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To answer the second question a survey was undertaken of the pyrexial diseases listed in the text books of medicine. This survey has shown that the Time Factor can be used to classify the febrile affections into the following 2 groups: 1. Those which develop distinctive symptom patterns within a period not exceeding 10 days, and usually within the first week, from their onset. 2. Those which continue their febrile course past the tenth day without the emergence of clinically demonstrable localizing features despite detailed daily bedside examination. Some of these conditions, for example Brucellosis, are characterized by periodic pyrexial episodes of variable duration as well as by prolonged fever. It is necessary to underline the phrases "distinctive symptom patterns" on the one hand, and "clinically demonstrable localizing features" on the other. Generalized myalgic pains, vague joint pains, lumbar backache, headache, nausea, vomiting, constipation, diarrhœa, cough, soreness of the throat, are transient symptoms common to the inaugural stages of febrile diseases in general. Any combination of these is, therefore, of no diagnostic utility. Similarly, fatiguability, pallor, anorexia, weight loss, unless this be unduly rapid, transient headache and, more particularly in children, ill defined abdominal pain with or without nausea and vomiting, are common accompaniments of a prolonged elevation of the temperature from any cause and have, therefore, no specific localizing value.

In some of the conditions of Group 2 fever of more than 10 days duration or repeated pyrexial bouts is the usual clinical presentation, e.g. Brucellosis. In others, prolonged or recurring pyrexia without localizing signs or symptoms constitutes an atypical clinical expression of the disease, e.g. Rheumatic Fever. In order that no known cause of obscure fever may be inadvertently left out of consideration a comprehensive study of the literature was undertaken with special reference to such atypical manifestations of the more common diseases.

To the first group belong the vast bulk of pyrexial conditions such as Measles, Lobar Pneumonia and the like met with in everyday clinical practice. In the second group it has been possible to place 51 diseases, a classified list of which is shown in Table I pages 4 and 5. Although it is not intended to imply that this list is completely exhaustive, it constitutes a comprehensive practical guide to the possibilities to be considered in the differential diagnosis of a given case of fever which either continues past the 10th day or recurs in cycles of variable duration without the emergence of localizing symptomatology.

Considered from the prognostic point of view this collection will be found to include the following conditions:- 1. Diseases, such as Acute Leukaemia, which are attended by an inevitably fatal outcome.

TABLE I. CLASSIFIED LIST OF THE DISEASES

GROUP I

THE SPECIFIC INFECTIONS

	(a) Coccal Infections	(b) Bacillary Infections	(c) Virus Infections	(d) Rickettsial Infections	(e) Spirochætal Infections	(f) Protozoan Infect
of the Cardiovascular System	1. Rheumatic Fever 2. Subacute Bacterial Endocarditis					2.
of the Respiratory System		4. Chronic Fibrocaseous Pulmonary Tuberculosis 5. Tuberculosis of the Mediastinal Lymph Glands	12. Primary Atypical Pneumonia			23
of the Nervous System		6. Tuberculous Meningitis	13. Lymphocytic Choriomeningitis			24
of the Digestive System		7. The Enteric Fevers				25 26 27
of the Hæmopoietic System		8. Tabes Mesenterica				
of the Urinary System						28. 29.
of the Locomotor System						30.
Without Specific Anatomical Localisation	3. Septicæmia	9. Brucellosis 10. Acute Miliary Tuberculosis 11. Chronic Miliary Tuberculosis		14. Epidemic Typhus 15. Endemic Typhus 16. Tick Typhus 17. Mite Typhus	18. Secondary Syphilis 19. Relapsing Fever	20. Malaria 21. Visceral Leishmania

PRESENTING WITH OBSCURE FEVER

GROUP 2 Deep-seated Suppuration	GROUP 3 Malignant Neoplastic Diseases	GROUP 4 Blood Dyscrasias	GROUP 5 Helminthic Infestations	GROUP 6 Conditions with Heterogeneous Etiology
22. Pyogenic Lateral Sinus Thrombophlebitis				41. da Costa's Syndrome 42. Periarteritis Nodosa 43. Acute Disseminated Lupus Erythematosus 44. Chronic Subdural Hæmatoma in Infants
23. Encapsulated Empyema				45. Chronic Nasopharyngitis
24. Brain Abscess				46. Neurogenic Fever 47. Pink Disease
25. Subphrenic Abscess 26. Retrocæcal Appendix Abscess 27. Liver Abscess	31. Carcinoma of the Stomach			48. Regional Ileocolitis
	32. Lymphosarcoma of the Mediastinal Glands	34. Infectious Mononucleosis 35. Infectious Lymphocytosis 36. Acute Aleukæmic Leukæmia 37. Hodgkin's Disease	38. Filariasis Nocturna	
28. Perinephric Abscess 29. Renal Carbuncle	33. Hypernephroma		39. Schistosomiasis	
30. Deepseated Osteitis			40. Trichiniasis	
				49. Drug Fever 50. Bed Fever 51. Spurious Fever

2. Diseases which leave crippling sequelae in their wake, e.g. Rheumatic Fever. 3. Affections which are curable by early treatment, e.g. Amoebic liver abscess. 4. Conditions which are either self-terminating, e.g. Primary Atypical Pneumonia, or are not necessarily self-terminating but remain organically innocuous, e.g. da Costa's Syndrome. The significance of considering the prognostic aspect of the obscure fevers lies in the fact that, should a diagnosis be unattainable within a reasonable period of time, it will be justifiable to give the assurance that, in all probability, no cause has been left out of consideration which responds to early treatment or which is likely to prove either crippling or fatal. For it must be frankly admitted that now and again a case of obscure fever will be encountered which defies our best efforts at a diagnosis. Alt and Barker[2], for instance, refer to a case in which the cause of the pyrexia remained obscure after 13 years observation in many institutions, while Hamman and Wainwright[33] recall the case of a young woman in whom continued low grade fever had been present for almost 25 years. There are, indeed, as is well known, instances where the cause of an obscure fever cannot be revealed even at autopsy. Parenthetically, it may be pointed out that, generally speaking, the patient who presents with prolonged pyrexia as the major manifestation of his malady is an early case. This statement carries with it 2 implications:- 1. The practical importance of a diagnosis at this stage, for many of the diseases

listed as presenting with obscure fever are amenable to cure by timely treatment with the danger of serious complications arising if treatment is delayed till the disease has reached its clinical threshold, e.g. Amoebic Liver Abscess, Hypernephroma and the like. 2. The exclusion from the differential diagnosis in a given case of cryptic fever, of conditions, like malignant neoplastic disease of the liver, which may be attended by pyrexial episodes, but which are then almost always in their advanced stages, bearing clinical marks by which they may be recognized or suspected.

And now a word about the classification. The set up is both anatomical and etiological. Neither component of this classification is, however, intended to be the answer to a diagnostic grouping of the obscure fevers. The corner stone of such a diagnostic grouping is, as will be shown in part 2 of this thesis, the Serial Hæmogram. The present scheme is designed mainly to reflect the possibilities in an orderly fashion.

Primary Atypical Pneumonia appears under the virus infections because, although the causal agent has up to the time of writing, not been isolated, it is the current view that a virus is probably responsible. Trichiniasis has been placed opposite the locomotor system because the major impact of the infestation is on the voluntary muscles. Da Costa's Syndrome, etiologically probably more correctly a form of neurogenic fever, finds a position opposite the cardiovascular

system in view of symptomatic reference to the heart. Although recent work has shown that Disseminated Lupus Erythematosus is a lesion of the connective tissue rather than a diffuse vascular disease, it has been thought more appropriate to place it opposite the cardiovascular system in view of its association, in some 30% of cases, with Libman-Sacks verrucous endocarditis and a cardiac murmur. It will be observed that a separate heading is accorded to deep-seated abscesses despite the fact that these conditions could well be included under the specific (largely coccal) infections. The reason for this subdivision is essentially practical. For, apart from the fact that deep-seated suppuration has a world wide incidence as a common cause of obscure fever, the group lends itself, as will be shown later, to a relatively simple exclusion on the basis of the clinical history and the peripheral blood picture.

Finally, attention must be directed to a notable omission, namely that of a special anatomical group for the chronic infective foci. The reason is, that a study of the literature has brought only one convincing report of focal infection as the cause of prolonged fever without localizing features. It is that of O'Connor,[63] who calls attention to chronic naso-pharyngeal infection as a common cause of continued otherwise unexplained low grade fever. (vide p 35). Kintner and Rowntree[43] studied 100 cases of obscure fever at the Mayo Clinic from June 1919 to June 1930. The question of a chronic focus of

infection was raised. A focus was found in 35 of their cases and removed. This resulted in the subsidence of the pyrexia in 60% of the 35 cases. They also found, however, that in an almost equal number of patients in whom no foci were found, the fever subsided in 59% of the cases. They conclude, therefore, that the removal of an infective focus does not affect the recovery rate. The writer's own experience is in complete accord with that of Kintner and Rowntree that an infective focus, when found, is with the possible exception of chronic nasopharyngitis, in all probability unrelated to the cause of the fever.

We now come to the detailed consideration of each of the disease entities listed in the classified collection in Table I with special reference to the thesis that all are potentially responsible for the clinical presentation with obscure fever.

1. Rheumatic Fever may set in and continue with pyrexia as the only significant clinical expression of its existence. This atypical form (subacute rheumatism) is common in children and not infrequent in the second and subsequent attacks of polycyclic rheumatism in young adults. The temperature is seldom elevated above 100°F and the fever may be continuous or in the form of recurring bouts of up to 7 days duration interspersed with 7-14 days afebrile intervals. Throughout its course, which may endure for "weeks or months or even years," (White[86]) the collateral clinical manifestations are nothing more than the common accompaniments of a prolonged febrile illness: fatigue, anorexia,

weight loss, slight pallor, mild sweats and ill defined aches and pains in body and limbs. Migratory polyarthralgia, chorea, rheumatic nodules and erythema marginatum are notably absent throughout. "The rheumatic nature of the disease is often overlooked and, in fact, could be suspected only by the most careful consideration of the secondary factors of rheumatism." (Levine[47]).

2. Subacute Bacterial Endocarditis. The diagnostic tetrad of infective endocarditis is prolonged fever, a cardiac murmur, embolic phenomena and a positive blood culture for streptococcus viridans. In private practice the victims of infective endocarditis are usually first seen presenting with continued fever without clinically demonstrable embolic manifestations and often with negative blood culture. The diagnosis of infective endocarditis cannot be seriously considered in the absence of a cardiac murmur. For while it is theoretically possible for streptococcus viridans to engraft itself upon a clinically silent rheumatic mural endocarditis or upon a congenital bicuspid valve, it is generally agreed that, by and large, the organism settles on a clinically demonstrable congenital or rheumatic cardiac valvular lesion or upon an arteriovenous communication either central, such as a patent ductus, or peripheral. (Lipton and Miller[48]). On the other hand, if the only demonstrable murmur is systolic in time and soft, or only moderately loud in intensity, the question arises whether it is to be regarded as organic or whether it is

merely an expression of the anæmia which is common to infective endocarditis and to a host of other obscure fevers. Thus, while the detection of a murmur in a given case of prolonged fever suggests subacute bacterial endocarditis as a possibility, the murmur cannot be taken as prima facie evidence of its existence.

3. Septicæmia. There are atypical examples of Acute Septicæmia which run their entire course to death or recovery without conspicuous rigors or excessive sweating and without clinically demonstrable involvement of the joints or of any of the other serous cavities. The temperature, instead of being of the classical swinging picket-fence type may be irregularly remittent with only occasional spiking. The spleen, though always affected at necropsy, is often too soft to be palpable clinically. Furthermore, in about 10% of cases[40] there is no detectable portal of entry of the organism into the circulating blood. Keefer[40] in his comment on a case of septicæmia presenting with prolonged pyrexia as the only clinical manifestation, reminds us of the "importance of making blood cultures in patients with fever of obscure origin." The diagnosis of this case was made in the 4th week by hæmoculture.

A chronic form of septicæmia due to Neisseria intracellularis, often referred to as Chronic Meningococcæmia, is being "recognized with increasing frequency during the past few years ... as one of the most common types of disease produced by the meningococcus." (Kinsman and

D'Alonzo[42]). In its characteristic form, pyrexia, chills, rash and arthralgia constitute a syndrome which is almost pathognomonic of the disease. But, whereas pyrexia is always present, the rash "which is a sine qua non for making the diagnosis clinically,"[42] the arthralgia and the chills may all be absent. Thus in the 88 cases of meningococcæmia reported by Campbell[11] rash was absent in 10, arthralgia in 33 and chills in 40. "Several authors in the past 5 years have been specific in denying the presence of a rash. In 10 case reports out of a total of 88 (11.4%) there was no mention of rash. This ... is an important and encouraging change which supports the idea that blood cultures should be repeatedly made in all instances of obscure fever."[11]

4. Chronic Fibrocaseous Pulmonary Tuberculosis. With routine radiography of the chest the pyrexia of chronic fibrocaseous pulmonary tuberculosis is not likely to remain obscure for any length of time. It is a well known fact, however, that persistent fever or recurring febrile bouts of short duration may dominate the clinical picture of chronic phthisis. Borowitz and Dwork[8] remind us that in the diagnosis of tuberculosis "physical findings are totally unreliable," and that "changes in fremitus, dullness and breath sounds are not significant enough to be considered." In a study of minimal tuberculosis these observers found apical crepitations - the most valuable diagnostic sign - in only 57 out of 200 of their cases (29%). Cough may be minimal and unproductive; 2% of Borowitz and Dwork's patients gave no history whatsoever of cough.

5. Tuberculosis of the Mediastinal Glands. Active tuberculous lymphadenitis of the mediastinal nodes may exist without any significant clinical features other than continuous or recurring low grade fever. Paroxysmal brassy cough is, in the experience of most clinicians, quite infrequent, and clinical evidence of mediastinal compression is extremely rare. The expected paravertebral and parasternal dullness and d'Espine's sign are rarely to be found, and physical examination in general is, as a rule, quite unhelpful. The diagnosis of mediastinal tuberculosis in one of Keefer's[40] cases of unexplained fever was suspected by the radiographic demonstration of enlarged hilar glands and confirmed by biopsy of a gland which appeared in the anterior triangle of the neck on the 16th day after admission to hospital.

6. Tuberculous Meningitis. Although tuberculous meningitis is preceded by a tuberculous lesion elsewhere in the body, usually in the lungs, the primary focus, wherever it may be, is more often than not clinically silent. Moreover, signs referable to the nervous system are classically delayed for a period of 2 to 6 weeks. During this so called prodromal stage low grade irregular fever dominates the clinical picture.

7. The Enteric Fevers. Of all the conditions which have been listed as potential causes of prolonged fever without localizing signs or symptoms, typhoid or any of its 3 congeners is usually the first to be suspected. It is well known that the disease may run its entire course

without the appearance of rose spots, without the passage of pea soup stools, and without clinically demonstrable splenomegaly. Furthermore, even if routine blood culture were feasible in general practice in all cases of pyrexia which continue to manifest no localizing features for 5 or 6 days, this would still fail to remove enteric from the realm of obscure fevers, since blood culture is not universally positive even when the blood is examined at the optimum period, namely the 5th or 6th day from the onset. Finally, typhoid in relapse, especially when the original attack has been a mild one, may give rise to an indefinite pyrexial illness lasting many weeks without a single clinical clue to suggest the cause. (Cabot[9]).

8. Tabes Mesenterica. "Tuberculous glands in the mesentery are often overlooked for the very good reason that they may give no definite signs." (Douthwaite[18]). Madding[52] reports a case of tabes mesenterica proved by exploratory laparotomy and biopsy, the patient having run a temperature for over 8 months without localizing signs or symptoms. Because of an associated symptomatic reference to the right upper quadrant hepatic amoebiasis was suspected, but neither the temperature nor the symptoms responded to a full course of specific treatment for this condition.

9. Brucellosis. The best time, indeed the only time, to establish the diagnosis of undulant fever is during the first week of the initial attack by hæmoculture. Brucellæ have been recovered by blood culture

as early as the second day. After the first week of the initial attack the laboratory is often incapable of providing convincing evidence for or against brucellosis for the following reasons:- (a) Something like 10% of culturally proved cases never develop agglutinins. (Foshay[26]). (b) The finding of specific agglutinins, even in high titre, in a suspected case of brucellosis is analogous to the finding of a positive tuberculin test in a suspected case of tuberculosis: it connotes tissue invasion but cannot be taken as conclusive evidence of the existence of active disease. (c) The search for the diagnostic rising titre may be doomed to disappointment for, in place of a sustained rise in the titre, "agglutins may appear intermittently at irregular and unpredictable intervals."[26]

10. Acute Miliary Tuberculosis is to be counted among the first possibilities to be considered in a given case of persistent pyrexia without positive clinical findings particularly when the patient is an infant or young child. No age is, however, immune and even old age is no insurance against the infection. "Acute generalized miliary tuberculosis is by no means unknown in the seventh, eighth and ninth decades." (Chapman and Whorton[13]). It is true that the lungs are affected with great frequency and at an early stage. But it is also true that both cough and physical signs in the chest may be completely absent. Thus cough was persistently absent in no less than 18% of Chapman and Whorton's[13] series throughout the course of the disease,

while involvement of the lungs was found at autopsy in 65% of the cases. The spleen and liver share with the lungs both the frequency of involvement as well as the accessibility to clinical examination. But it is the general experience of clinicians that gross splenomegaly is rare in miliary tuberculosis and enlargement at autopsy does not necessarily mean that the organ was palpable during life. With regard to the liver, the finding of clinical hepatomegaly, when the enlargement is not outspoken, is notoriously subject to differences of opinion. Localizing signs may, therefore, be notably absent despite the almost universal impact of the miliary process upon clinically accessible organs.

11. Chronic Miliary Tuberculosis. Chronic miliary tuberculosis may start insidiously with continued low grade fever, minimal constitutional disturbance, unproductive cough, remarkably little wasting, no clubbing and repeatedly negative findings on clinical examination including that of the chest. (Hoyle and Vaizey[37]).

12. Primary Atypical Pneumonia. We are of recent years becoming alert to the possibility of primary atypical pneumonia in patients presenting with prolonged fever (4 to 6 weeks or longer) more especially when there is an accompanying cough without abnormal physical signs in the chest. While the absence of chest signs is a recognized negative feature of the disease, it is necessary to underline the remarkable fact that there may be no cough at all throughout the entire course of the illness

despite radiographic evidence of parenchymal or adnexal involvement of the lungs. Schmitz[76] found 15% of cases without cough, while 8 out of Gundersen's[31] 122 patients had no cough. Two of the writer's own cases had only an occasional unproductive cough in the course of a 4 weeks' febrile illness. There may, indeed, be no localizing signs whatever to afford a clue to the diagnosis. As Schmitz[76] points out the physician may be consulted only for the fever or because the patient is too weak to go to work.

13. Lymphocytic Choriomeningitis. The appearance of signs of meningeal irritation in lymphocytic choriomeningitis may be delayed for a period of up to 21 days. (Farmer and Janeway[24]). During this prodromal phase pyrexia unaccompanied by any positive clinical findings is the presenting feature of the disease.

14-17. The Rickettsial Diseases. Since the rash is a characteristic feature of the rickettsial diseases, while the bite of the insect vector is a notable physical sign in the tick and mite borne groups, why, it may be asked, are these diseases to be included amongst the obscure fevers? The answer is as follows:- (i) In epidemic (louse borne) typhus "the eruption may never appear, especially in children." (Harries and Mittman[35]). (ii) In endemic (flea borne) typhus "the rash ... may comprise only a few macules which may disappear in a day or so" (Dyer[20]) and thus pass unnoticed. (iii) In African tick-bite fever

"it must be noted ... that an appreciable percentage of cases develop no rash." (Elliott[21]). (iv) In scrub (mite borne) typhus Machella and Forrester[51] detected a rash in 51.5% of cases, the remainder running their course without an eruption. (v) In Q fever there is never a rash in either of the two clinical varieties. Finally, we have in South Africa to contend with the question of skin colour, for in the coloured races an exanthem is notoriously easy to miss.

A primary sore indicative of the bite of the insect vector is to be expected in the tick borne and mite borne groups. But this is by no means invariably present. Thus, in Machella and Forrester's[51] series of 64 cases of scrub typhus no fewer than 21 (33%) showed no evidence of the bite of the insect vector. Speaking of African tick-bite fever, Elliott[21] in a clinical study of 296 cases found no evidence of a bite in 4. He points out that the bite may be atypical and insignificant in size and, therefore, readily misinterpreted.

Generalized peripheral lymphadenopathy and splenomegaly occur in tick and scrub typhus, but by no means invariably. Machella and Forrester[51] report absence of adenopathy in 4 out of their 64 cases of scrub typhus and no demonstrable splenomegaly in about 50%. Elliott[21] records an absence of adenopathy in 95% while the spleen was palpable in only 4 of his 296 cases. In the other rickettsial diseases adenopathy and splenomegaly are extremely rare. Regional lymphadenitis, whether the bite is clinically demonstrable or not, is always present.

If, however, the reaction to the bite is atypical the sore plus the regional lymphadenitis may be mistaken for a pyogenic infection.

The Weil-Felix test is incapable of deciding upon the presence or absence of a rickettsial infection during the first 10 days of fever for the following reasons:- (i) The test may remain persistently negative in a percentage of cases of all the rickettsial diseases including epidemic typhus. The diagnosis in these cases has been proved by the recovery of rickettsiæ by intraperitoneal injection of mice with the patients' blood. (ii) In the tick and mite borne groups a positive Weil-Felix is usually only to be expected late in the second week of the illness, and not infrequently it is delayed till defervescence.

18. Secondary Syphilis. Remittent or intermittent fever lasting 2 or more weeks may be the dominant outward sign of secondary syphilis when, as sometimes happens, the eruption fails to appear, the generalized lymphadenopathy is inconspicuous and condylomata and mucous patches are absent. Sore throat, while usually complained of, may be slight and examination of the oropharynx may fail to disclose spectacular snail track ulceration. Furthermore, a history of a primary sore may not be forthcoming, especially in women and also in men with an intrameatal chancre while an extragenital chancre often passes without suspicion. Latent syphilis may also give rise to long continued fever without localizing symptomatology.

19. Relapsing Fever. In its classical form relapsing fever is characterized by pyrexial bouts which vary in duration from 1 to 7 days (average 2 or 3 days) separated by afebrile intervals of from 1 to 42 days duration (average 3-5 days). There are, however, atypical forms in which the pyrexia continues in an irregularly remittent fashion for a period of 2 to 6 weeks unaccompanied either by an eruption or by splenomegaly. Two of Wood and Dixon's[94] 12 cases had these "long periods of low continuous fever" unaccompanied by any physical signs: no rash and no splenomegaly.

20. Malaria. It is a well known fact that the classical tertian or quartan periodicity of malaria is often replaced by continuous fever. The spleen, though usually enlarged, is often not palpable because of its softness. To add to our difficulties, antimalarial self medication or suppressive treatment or both is almost universally practised by patients hailing from the tropics. This procedure, not only interferes with the natural course of the disease but renders it difficult or even impossible to demonstrate the parasite in the peripheral blood. Furthermore, no previous history of malaria may be forthcoming for the following reasons:- "Those who have taken quinacrine regularly and in sufficient amounts for effective suppression will give no history of malaria while overseas." (Most and Hayman[59]). (ii) Patients with a history of residence in malarious areas, though infected, often suffer their first attack of malaria either after the lapse of the incubation

period (10-14 days) or as long as 12 months after returning to their non-malarious domicile. These so called delayed primary attacks are due to the practice of suppressive medication while in tropical residence followed by discontinuance on return home. They are most commonly due to P.vivax. "The onset of the disease in this group ... does not conform to that usually associated with malaria. The disease may begin insidiously with malaise and headache. The temperature, which is elevated slightly at the onset, rises gradually or abruptly within a few days to 103 or 104°F, and the pattern of the temperature may be completely irregular or of the septic remittent type. Severe shaking chills ... may be absent. Further ... one or two routine smears made early may be negative for malarial parasites. We have seen patients with delayed primary vivax malaria who had negative thick smears when examined twice daily for 2-5 consecutive days, despite high fever, before parasites could be demonstrated. Unless one is familiar with such modes of onset the diagnosis of vivax malaria may not be suspected, correct treatment will be delayed and in some instances other treatment potentially dangerous to the patient may be instituted." (Most and Hayman[59]).

Speaking of subclinical malaria, which may present with prolonged low grade fever, Ferriman[25] points out that splenomegaly can be detected in only 1/3 of the cases, the general condition is good, t here is no impressive anæmia and blood slides are usually negative.

He suggests that these subclinical forms are probably due to incomplete suppressive medication or to inadequate natural immunity.

Finally, there are two other contingencies which bring malaria into the realm of continued fevers, namely, superimposed infection with two or more generations of parasites maturing on successive days and repeated infection by fresh broods of parasites in those resident in malarious areas.

21. Visceral Leishmaniasis which is characterized by recurring bouts of pyrexia lasting from 2 to 6 weeks separated by apyretic intervals of varying duration may present with fever only in the first or second of these pyrexial episodes. Thus, during the initial and at least one subsequent attack there may be no splenohepatomegaly, no significant peripheral lymphadenopathy and no dusky pigmentation of the skin, fever alone being the presenting manifestation of the disease.

22-30. Deep-Seated Suppuration. The following comments are in support of the inclusion of the 9 examples of deep-seated suppuration as potentially responsible for prolonged fever of obscure nature. They are considered seriatim in the order in which they appear in Table I Group 2 (p 4-5).

"The syndrome of lateral sinus thrombosis tends to be obscure ... and ... the lesion can occur without distinctive signs or symptoms." (Kinnier Wilson[87]). Encapsulated empyema bears no physical

marks by which it may be recognized; its presence can only be demonstrated by expert radiology. Cabot[9] describes a case of post-pneumonic interlobar empyema presenting with pyrexia without localizing signs the diagnosis having been finally established, about 6 weeks after the inception of the fever, by the 5th paracentesis of the chest. Speaking of intracranial abscess Kinnier Wilson (loc cit p 192) points out that "except perhaps at a late period the abscess syndrome is not so clear cut as to promise ready distinction from other infective lesions." That subphrenic abscess may, and usually does, present with pyrexia without decisive localizing symptomatology needs no special emphasis or illustration. Douthwaite[18] records a case of appendix abscess where the patient ran an irregular temperature for 12 days without the emergence of localizing symptomatology, the mass remaining undemonstrable until the 13th day from the onset of the fever. The liver is one of the commonest sites of deep-seated suppuration. The commonest cause in South Africa is the entamoeba histolytica. Keefer[40] reports a case of latent diverticulitis of the large intestine with metastatic abscesses in the liver presenting with obscure fever. This entity must be extremely rare since, as Keefer himself points out, only one other case could be found in the English literature, and as long ago as 1906. Speaking of amœbic liver abscess Sodeman and Lewis[78] share the common experience that there may be "a lack of localizing signs in the liver so that the differential diagnosis involves the consideration of febrile disease without localizing

signs ... conditions which fall into a group called fever of undetermined origin." In 12% of Sodeman and Lewis' cases hepatomegaly could not be elicited in the presence of continued fever and leucocytosis. Deep-seated osteitis, usually affecting the pelvic girdle is not an infrequent cause of obscure fever largely in children. In Perinephric Abscess and Renal Carbuncle the appearance of unequivocal costovertebral angle signs and symptoms is almost universally delayed for at least 2 weeks and often for 3 weeks or even longer. The writer suspected the existence of a perinephric abscess as the cause of prolonged cryptic fever in a European male J.K. 18 years of age because of the persistent neutrophil leucocytosis with left shift and toxic granulation coupled with a history of furunculosis. The loins were, therefore, repeatedly examined for tenderness and fullness in the course of the daily routine bedside study and yet it was only on the 24th day that unequivocal tenderness without fullness could be detected. The parents refused to permit hospitalisation. They, however, consented to an x-ray examination and the boy was taken by ambulance to a radiologist. The suspicion was confirmed radiographically by the demonstration of fuzziness of the homolateral psoas outline, together with elevation and restricted movement of the ipsilateral hemidiaphragm. Over a pint of pus under tension was evacuated at operation. It may be of interest to record the follow up of this case. The temperature failed to subside and the blood count continued to show a neutrophil leucocytosis. Blood culture was negative and there was no blockage of the drainage tube.

A complicating subphrenic abscess was suspected and it was decided to needle the subdiaphragmatic space, the surgeon having made preparation to resect a rib. Needling was positive, a rib resected and about a cupful of pus was evacuated from beneath the diaphragm. The temperature and leucocytosis rapidly subsided and the patient made an uneventful recovery.

31. Carcinoma Ventriculi. Rigler and his co-workers[73] declare that "the presence of a moderate or even large carcinoma of the stomach in a patient without any gastric symptoms whatever is a common experience." In these cases the growth usually arises in the fundus and, although anorexia and some weight loss are usually present, there may be no symptoms referable to the digestive system. Occasionally these patients present with prolonged fever as the predominant clinical expression of their malady. It has, however, been possible to find only one reference in the literature of this presentation, namely that of Keefer[40] who, in a study of 80 cases of obscure fever, found cancer of the stomach to have been responsible for 2 of them. The record and discussion of a case investigated by the writer will be found in section (c) of part 2 of this thesis.

32. Lymphosarcoma of the Mediastinal Glands. Lymphosarcoma may, like Hodgkin's Disease, primarily affect the mediastinal glands where it may remain localized for a time without clinically demonstrable involvement of the peripheral lymph nodes and without the mediastinal syndrome.

The spleen is rarely, if ever, enlarged. While lymphosarcoma is a relatively common disease, the presentation with fever is rare "except in the occasional forms of the disease, usually in children, ... in which fever may be the most prominent symptom." (Jackson and Parker[39c]).

33. Hypernephroma. It is common knowledge that the course of malignant neoplastic disease may be attended by pyrexial episodes or by protracted fever. But in the vast majority of these cases, when fever makes its appearance the disease is already far advanced showing clinical features which are more outstanding than the pyrexia. Occasionally, however, continued fever may be the initial and only outward sign. Hypernephroma is amongst the commonest of the malignant tumours to manifest itself clinically with prolonged fever. Thus, in Hamman and Wainwright's[33] study of 90 patients with prolonged cryptic fever, no fewer than 7 (about 10%) turned out to be hypernephromata. This tumour was also found to be the cause in 3 of Keefer's[40] 10 cases of prolonged unexplained fever due to neoplastic disease. Soloway[79] in a review of 130 cases of renal tumour declares: "The symptoms of renal tumour vary greatly, and, although the classical triad - haematuria, tumour and pain - is most frequently mentioned and sought for, yet it was present in only 27 or 17% of the cases. There were 32 patients who gave no history whatever of urinary symptoms and repeated urinary examinations were negative for red blood corpuscles." Ljunggren[49] in his report of a case of hypernephroma with fever as the only manifestation for a period of about 5 months, points out that "fever may

constitute the first, and, for a long time, the only clinical manifest symptom of renal tumour." Hypernephroma as a cause of prolonged unexplained fever seems, therefore, of sufficient frequency to merit serious consideration, more especially in patients in the 5th and 6th decades.

34. Infectious Mononucleosis is a highly prevalent disease with a most baffling array of clinical variants. Bernstein[4] in his classical monograph enumerates no less than 29 conditions which it may simulate. We are here, however, only concerned with Tidy's[84] "febrile type" of the disease. This febrile aglandular type, may be completely silent clinically with a total pyrexial period of up to 2 months duration with the liability to recrudescence. (Reyersbach and Lenert[72]). The Paul-Bunnell test may be negative, the latest statistics placing the positive results in clinico-haematologically proved cases at no higher than 60%. Moreover, this test may be positive only transiently and at unpredictable intervals during the course of the disease.

35. Infectious Lymphocytosis is a term introduced by Smith[77] in 1941 to describe a new febrile illness unaccompanied by any specific symptoms or physical signs, and featuring a conspicuous absolute lymphocytosis in the peripheral blood. The lymphocytes are all of the small variety with perfectly normal morphological characters. The heterophile agglutination test for sheep's erythrocytes is uniformly negative in these cases. Smith describes 2 types, acute and chronic. The acute

form does not concern us here since the pyrexia usually subsides within 48 hours, although the lymphocytic leucocytosis persists for 3 to 5 weeks, during which period the patient is perfectly well. The chronic form is a typical example of obscure fever, the temperature remaining elevated in an irregular fashion for weeks or months on end without any remarkable symptomatology. In one case the fever continued for 4 years. All the patients in Smith's series were infants or children between 7 months and 11 years of age. More recently the chronic form has been reported also in young adults. Duncan,[19] although heading his article "Acute Lymphocytosis in Young Adults" presents 2 cases, one of which (Case I) is actually a record of the chronic form.

36. Acute Aleukaemic Leukaemia. Acute leukaemia often opens the clinical picture with pyrexia as the cardinal sign, especially in children. Physical examination may be completely negative for a considerable period and sometimes throughout the entire course of the disease. While the diagnosis of the leukaemic form is usually readily established from an examination of the peripheral blood alone, the identification of the aleukaemic types often presents considerable difficulty. These aleukaemic examples are said to make up some 10% of cases of acute leukaemia, most of which are of the myelogenous variety. Bomford & Rhoads[7] classify aleukaemic leukaemia into (i) leucopoenic forms -

low total white cell counts with primitive cells present in the peripheral blood, and (ii) aleukaemic forms - low total counts with no abnormal leucocytes in the peripheral blood. It is the latter variety of aleukaemic leukaemia which causes the greatest difficulty in diagnosis, for apart from the leucopoenia there may be "no alterations whatever in the cellular elements of the blood." (Wiseman[91]).

37. Hodgkin's Disease may start in the mediastinal or abdominal lymph nodes. Peripheral lymphadenopathy may fail to appear in these cases for as long as 6 months. (Jackson and Parker[39a]). Meanwhile, continued or recurring fever may be the only outward manifestation of the disease.

In their discussion of mediastinal Hodgkin's Jackson and Parker in a series of 7 papers covering the various aspects of 213 cases of Hodgkin's Disease stress the following points which are pertinent to our discussion:- (a) "Fever may be the presenting and, indeed, the only symptom for weeks or months."[39c] (b) In 18 out of 90 cases of initial mediastinal Hodgkin's, symptoms were entirely absent.[39b] (c) Two patients presented with pyrexia only for as long as 6 months.[39a] (d) One patient who came to autopsy "showed involvement of the para-aortic and peribronchial lymph nodes without the slightest evidence of Hodgkin's granuloma elsewhere."[39b] (e) "It is often difficult to detect even a large mediastinal tumour by physical signs alone, and since the development of the full-blown mediastinal syndrome may be delayed for weeks or months, a clinical diagnosis may be impossible for an equal

period of time."[39b] (f) In dealing with the radiographic evidence these observers point out that "early involvement of the mediastinal lymph nodes may be completely masked in the frontal plane by the normal shadow of the heart and great vessels and ... lateral and oblique views ... show only an increase in the hilar shadows in the early stages."[39b]

Speaking of the abdominal form of Hodgkin's Keefer[40] points out that "prolonged fever without localizing signs" is one of the clinical manifestations of this form of the disease. "There is no group of diseases," he declares "in which the diagnosis is more difficult than that with involvement of the lymph nodes of the abdomen without demonstrable lymph node involvement elsewhere. This occurs in about 10% of the cases ... Without an operation or the development of enlarged lymph nodes in the periphery the diagnosis of abdominal Hodgkin's disease may be impossible."

Thus, while it is true that "well over 90% of all cases of Hodgkin's disease eventually show enlargement of the superficial nodes,"[39c] enabling a diagnosis to be established by gland biopsy, it is also true that, pending the emergence of peripheral node enlargement, primary mediastinal and primary abdominal Hodgkin's disease may present with continued or recurring (Pel-Ebstein or Murchison) pyrexia, and that this presentation may, according to Jackson and Parker,[39a] continue for as long as 6 months.

Apart from the primary mediastinal and primary abdominal forms there is yet another type of Hodgkin's disease which may present with cryptic fever, namely, primary gastro-duodenal Hodgkin's granuloma (lymphadenoma). Jackson and Parker[39a] give the incidence of initial Hodgkin's disease of the stomach and duodenum as 4 cases out of a total of 174. "It seems clear" they say "that Hodgkin's granuloma occasionally occurs as a primary and possibly as an isolated lesion of the alimentary canal ... In the 174 cases followed ... the stomach was involved in 3 cases, the duodenum in 1 case, the sigmoid in 2, the cæcum in 2 and the œsophagus in 1 case ... the lesion proved at autopsy to be primary in the gastro-intestinal tract and confined almost entirely to the viscus concerned and the immediately adjacent lymph nodes, so that there seems to be some justification for speaking of the gastro-intestinal form of Hodgkin's granuloma." Hitherto no case of primary gastro-intestinal Hodgkin's presenting with cryptic fever has been recorded in any situation other than the duodenum - an autopsy verified case of which is described in Jackson and Parker's paper.[39a]

38. Filariasis Nocturna. Infestation with Wucheraria Bancrofti may give rise to, what Napier[61] calls, primary and secondary fever. Secondary fever, also known as Elephantoid fever, occurs in florid cases of filariasis showing the classical lymphatic œdema of the limbs and scrotum together with peripheral lymphadenopathy. It is probably due to secondary infection of the blocked lymphatic channels of the elephantoid skin. It is the primary form, or true filarial fever, which concerns us

here, since it is unaccompanied by any localizing features. It is said to be produced by the metabolites of the worm. The pyrexia is characteristically of the recurring type, each bout being often prolonged beyond 10 days with afebrile intervals counted in weeks, months or years. It is frequently mistaken for malaria which is endemic in the filarial areas for, like malaria, the febrile spells are accompanied by rigors with terminal diaphoresis.

39. Schistosomiasis is febrile during the anaphylactoid stage, i.e. during the period between invasion and the appearance of haematuria or muco-sanguineous diarrhoea, or both. The Japanese call this bilharzial pyrexia, Katayama. The fever may continue for a period of from 3 to 8 weeks. The urticarial rash, which is the only collateral manifestation, may be mild and evanescent disappearing within 2 days.

40. Trichiniasis or Trichinosis. Atypical cases of trichiniasis are not infrequently encountered where pyrexia, with fastigial levels up to 106°F, is the outstanding sign of the infestation. The temperature may remain elevated for more than two weeks. There may be no history of vomiting or diarrhoea. It is true that the peculiar oedema of the bulbar and palpebral conjunctiva is diagnostic of the disease. But this characteristic chemosis may be so inconspicuous as to pass unnoticed. This was so in 5 of the 11 cases of trichiniasis reported by Reifenstein et al,[71] and in one case of this series it was completely absent. The adult parasites are said to undergo digestion

in the small intestine. This probably accounts for the fact that parasites or ova are of infrequent occurrence in the stools.

41. da Costa's Syndrome. Friedman[27] has drawn attention to the fact that neurocirculatory asthenia can be associated with prolonged or recurring hyperthermia which is thought to arise from abnormal activity of the hypothalamus. Hamman and Wainwright[33] recall the case of a young woman 33 years of age in whom continued low grade fever had been present for almost 25 years. "The chief collateral features" they state "were palpitation, precordial pain, tachycardia and fatigue." The cause remained undiagnosed. In view of the associated symptoms it is more than likely that this was a case of da Costa's Syndrome.

42. Periarteritis Nodosa has been regarded until quite recently as an extremely rare disease. Only about 100 cases appeared in the literature from the time of Rokitansky's first description in 1852 till 1939. Since then case reports have been coming in from all parts of the world, so that by 1942 the recorded number of cases was 350 (Grant[29]) and the figures are still mounting. The mystery of its etiology remains unsolved. The general view today is that it is an allergic expression of the arterial system, occurring in the course of various infections and following the administration of certain chemotherapeutic agents, more especially the sulphonamides and animal sera.

Periarteritis Nodosa may manifest itself for a number of weeks through continued fever without decisive signs or symptoms to suggest

the diagnosis. One of the most illustrative examples of this presentation is the case recorded by Manson-Bahr.[53] "This most puzzling pyrexia" the author declares, "defied every means of diagnosis and remained insoluble until a biopsy of the gastrocnemius muscle ... revealed the true diagnosis." The fever continued with a mixed remittent and intermittent temperature curve for 3 months. "All possible investigations, including blood culture, lumbar puncture, complete x-ray and biochemical examinations were undertaken without any positive information being obtained ... The diagnosis was made shortly before death (three months after admission to hospital) and was completely vindicated at autopsy."

43. Acute Disseminated Lupus Erythematosus. Pyrexia is an outstanding clinical expression of disseminated lupus erythematosus. The fever which is usually irregularly remittent in character may continue for weeks or months on end. More usually, however, it is of the recurring type with spells of prolonged fever of variable duration, alternating with equally variable afebrile intervals. The characteristic butterfly erythema may fail altogether to appear, or may remain in abeyance for a long time. "We now recognize that it is possible to have hidden forms of disseminated lupus without the typical erythematous eruption and the butterfly distribution ... and that it is ... an entity that should be considered in the differential diagnosis of long continued obscure fevers." (Davenport[17]). In Blount and Barrett's[5] case the

appearance of the eruption was delayed for nearly 8 months from the date of onset of the disease.

44. Chronic Subdural Hæmatoma in Infants. The only symptoms of subdural haematoma in infants may be "a raised temperature, vomiting, irritability and failure to develop or gain weight ... there is no clinical picture which is absolutely characteristic of this lesion in infancy and neither the laboratory nor the x-rays help in the diagnosis." (Ingraham and Matson[38]). Ingraham and Matson point out (i) that subdural haematoma is common during the first 2 years of life, (ii) that temperature elevation is almost a constant feature, (iii) that it is due to falls on the frontal and occipital regions of the head with tearing of the tributary veins to the superior longitudinal sinus, (iv) that this type of fall is common, is apt to go unnoticed or be quickly forgotten by parents and nursemaids, and that the absence of a history of trauma should, therefore, never influence the diagnosis, (v) that suspicion of the diagnosis must rest primarily with the paediatrician and the general practitioner, and (vi) it is the source of a high morbidity if neglected.

45. Chronic Nasopharyngitis. O'Connor[63] calls attention to a series of 55 cases of prolonged unexplained fever referred to him by physicians, the fever having lasted between two weeks and seven years "without at any time presenting features ... which warranted a definite diagnosis." About three quarters of the cases "were known to have had

fever for at least three months." In all these patients, although the oropharynx and nose appeared normal, direct examination of the nasopharynx revealed unequivocal evidence of inflammation and nasopharyngeal swabs produced in 46% of the cases pure cultures of a single organism, e.g. Staphylococcus aureus. Local treatment, the technique of which is described, resulted in prompt subsidence of the pyrexia, resolution of the inflammation and "essentially negative cultures." The author feels that his study "may be of interest to any physician who encounters cases of low grade fever which fall into the category of fevers of unknown origin."

46. Neurogenic Fever. A considerable volume of literature has accumulated on the problem of neurogenic fever showing evidence that hyperthermia can occur solely on a psychogenic basis. From a study of the literature it has seemed convenient to classify neurogenic fever as follows: (a) Emotional deprivation in children. Bawkin[3] reports on 5 infants who were admitted to hospital for a non-pyrexial illness and there developed a persistent hyperthermia with fastigial levels between 101 and 103°F. "The infants did not appear acutely ill ... and a fairly good gain in weight was maintained." Careful clinical and special studies failed to reveal a cause for the persistently raised temperature. In all these infants the temperature promptly dropped to normal "within a few days of their return home." Bawkin concludes that the impersonal

environment of the hospital engendered emotional deprivation, and he believes this to be the mechanism of the production of prolonged fever since the pyrexia disappears as soon as the infant is returned to the personalized atmosphere of the home. (b) Repeated temperature readings. Horder has expressed the view that psychogenic fever may be engendered in nervous children whose temperature is taken daily by an over-anxious mother. We have repeatedly confirmed this impression in private practice. (c) "School Fever." Children who find the school situation unpleasant, especially when they show signs of emotional instability, not infrequently develop a temperature a few days before they are due to return to school, the hyperthermia continuing to a magic defervescence when the youngster is promised an extra week's holiday.

(d) Prolonged emotional tension. Wolf and Wolff[93] present the case of a man 43 years of age who, for a period of 13 years had frequently recurring bouts of fever up to 104°F. "At intervals during this time he was hospitalized and carefully studied at three large institutions."[93] No cause could be demonstrated. The patient was subjected by the authors to a careful personality study "during which a great many personality disorders were uncovered,"[93] largely involving prolonged emotional tension and anxiety. "He was given an opportunity to ventilate his conflicts and of resolving them. His fever stopped for a year."[93] The patient later suffered a recurrence which occurred in a setting of unusual anxiety and tension. The evidence adduced for the diagnosis of psychogenic fever in this case, which is magnificently worked up, is

so convincing that it would seem more than likely that some of the mysterious prolonged obscure fevers for which, after numerous investigations, no cause can be found, may be of this nature. (e) Hysteria. Manson-Bahr[53] records "an interesting case of hysterical mimicry associated with hectic fever in a nurse 32 years of age after reading that her brother had contracted meningitis." She developed all the signs of meningeal irritation. But, "in spite of everything her general condition remained good and lumbar puncture yielded a normal fluid."

47. Pink Disease (Infantile acrodynia). During the first 3 or 4 weeks of its course persistent fever with the usual morning-evening fluctuations is the usual presentation of Pink disease. There are no noteworthy collateral signs throughout the whole of this period and the symptoms during the first week or so are those of a "febrile cold." The pathognomonic red oedematous hands and feet do not appear till the second month of the illness.

48. Regional Ileocolitis. Sprague[81] and his associates report "a case of regional ileocolitis in which the diagnosis was obscured by an elevated temperature which persisted for some eight months before the usual clinical and radiographic signs appeared." The first suspicion of a localizing sign came 6½ months after the onset of the fever when, in the course of a routine physical examination, tenderness was noted in the right lower quadrant of the abdomen. A week later a

large peri-anal abscess and later a peri-rectal abscess appeared. These were the first exteriorizing signs of the disease. The authors stress the "need for considering this disorder in the differential diagnosis of obscure fever."[81]

49. Drug Fever. Prolonged fever may result from the administration of drugs, serum or whole blood. Among the commoner chemotherapeutic agents which may produce drug fever are the sulphonamides, gold, atropine usually in the form of eumydrine used in the medical regime for hypertrophic pyloric stenosis, pentnucleotide sodium, the organic arsenicals in syphilis, (Jarisch-Herxheimer reaction) the barbiturates, dinitrophenol self medication for slimming and thiouracil.

50. Bed Fever. Cabot[9] observes that "when fever persists beyond what we have reason to expect should be its natural term, we should always suspect that we may be dealing with a "bed fever." "Just what this means" he continues "we do not know, but its practical importance is due to the fact that it disappears when the patient gets up." Bed fever as a cause of continuous pyrexia should be considered especially in children when a mild low grade fever persists after recovery from an infectious disease. Douthwaite[18] points out that children may run a persistent temperature after the subsidence of an uncomplicated coryza and "if they be got up and sent about their ordinary life the fever commonly abates in the course of a day."

51. Spurious Fever. "The tricks for the production of pyrexia by the malingerer" says Douthwaite[18] "are legion." "One's suspicions are aroused" he continues "by the sight of a well nourished patient with normal pulse, no physical signs of disease ... and a temperature chart showing fever of several weeks duration." When spurious fever is suspected it is necessary to have "a nurse stay with the patient throughout the period during which the thermometer is registering, or take the temperature with the thermometer in the rectum." (Cabot[9]).

P A R T II

THE HÆMATOLOGY OF THE OBSCURE FEVERS

(a) Hæmatological Survey of the Obscure Fevers with Special Reference to the Importance of Serial Hæmography in the Elucidation of their Characteristic Blood Patterns

For the purpose of the hæmatological survey the diseases presenting with obscure fever will be considered seriatim in the order in which they appear in the classification shown in Table I pages 4 and 5.

1. Rheumatic Fever

The White Cells. Prolonged leucocytosis is a constant accompaniment of rheumatic fever. In the atypical forms, with which we are here solely concerned, the total count lies between 11,000 and 17,000 cells per cmm. with the majority of the counts in the vicinity of 12,000. While figures above 20,000 are often encountered in the presence of polyarthralgia, counts above 19,000 are rare in the atypical forms. (Swift et al[82]). The differential formula shows that the increase is due to a rise in the neutrophils to 80% or higher. The polymorphonuclear cells show moderate to marked left shift, all the shift cells being non-filamented neutrophils. Earlier forms, such as myelocytes, are hardly ever seen in rheumatic fever. An important negative hæmatological feature is the absence of evidence of toxic granulation in the neutrophils. Meranze and his associates[57] declare "no matter how ill the cardiac patient one should not expect to find toxic changes." The degenerative index was uniformly zero in their rheumatic fever patients.

Swift and his collaborators[82] have noted that, in the classical polyarthritic form, the administration of anti-rheumatic drugs, whether they be salicylates or the cinchophen group, tends to lower the white cell count whereas in the atypical forms (without arthralgia) drug therapy, while reducing the fever, is without effect on the leucocytosis which may continue for months in spite of continued medication. A further point of interest in this regard, and showing also the importance of the repeated blood count, is the finding by these observers that when a fall of the total count does occur with therapy in these cases it is only transient. "Counts must be made frequently enough, and over a sufficient period of time, to set forth the trend of the leucocyte curve." (Swift et al[82]).

The Red Cells and Haemoglobin. Pallor of the skin and mucous membranes, though seldom very marked, is always present in rheumatic fever. It is the clinical expression of the constantly occurring anaemia. As a rule the reduction of the haemoglobin is greater than that of the red cells resulting in a low colour index anaemia which, though characteristically progressive, is hardly ever intense. At its worst, the red cells are in the vicinity of 2.5 million and the haemoglobin 40%. Sometimes the anaemia is normocytic, i.e. there is an equal degree of reduction of the erythrocytes and of the haemoglobin.

Two other features characterize the anaemia of rheumatic fever: (i) it fails to respond to iron or liver, and (ii) it continues long after the temperature has subsided, i.e. the return of the red cells and haemoglobin to normal is remarkably slow.

The Erythrocyte Sedimentation Rate is markedly raised - 70 mm. or more by the Westergren technique. A raised E.S.R. occurs in almost any infection but the significant feature of the E.S.R. in rheumatic fever is that it often remains raised after the subsidence of the pyrexia.

2. Subacute Bacterial Endocarditis

The White Cells. In the great majority of cases of subacute bacterial endocarditis presenting with pyrexia as the major clinical manifestation, i.e. without clinically demonstrable embolic phenomena, the total leucocyte count lies within the normal range of 4,000 to 10,000 cells per cmm. If it rises at all, apart from clinically demonstrable infarction, it rarely exceeds 12,000. The lower limit is, however rarely under 5,000 and the upper rarely below 9,000. (Pepper[67]). With the advent of clinically recognizable infarction the total count rises, but usually no higher than around 20,000 (Pepper[67]) and with it the neutrophils. Minor embolic phenomena which are often impossible to demonstrate clinically, may raise the leucocytes to between 12,000 and 14,000 cells per cmm., the count returning to normal with the subsidence of the embolic shower. An important feature of the total count is its variability in the serial readings through a range of between 5,000 and 11,000 (Pepper[67]).

The differential formula reveals a slight tendency to neutrocytosis rarely, however, above 75%. Neutrophilia when present

is always absolute, since leucopœnia is never a feature of streptococcus viridans endocarditis. While the neutrophils may rise and fall with the rise and fall of the total count the remarkable feature is that in most instances this fluctuation does not proceed pari passu with the fluctuation in the total white cell count. Thus the total count is often at the upper limit of normal while the neutrophil percentage is at the lower limit of normal and vice versa, (Pepper[67]) or else the neutrophils may rise well above the normal maximum of 70% with a total count anywhere between the two normal extremes. "The differential count often remains more or less static for long periods irrespective of the total count." (Blumer[6]). The neutrophils are uniformly deviated to the left, i.e. there is an increase of the non-filamented forms above the normal maximum of 5%. (Osgood[66]). The degree of deviation is usually moderate to marked. (25 and 60% non-filamented forms). Neutrophil myelocytes, usually not exceeding 2%, occur in a few cases. Toxic granulation occurs late. (Kugel and Rosenthal[44]). It is usually absent in the preclinical stages.

The monocytes behave even more erratically than the total and neutrophil counts. An increase above the normal maximum of 10% will usually be found at one time or another when serial haemograms are made. It may be found in all specimens of blood taken or it may occur in one specimen or series of specimens and not in another.[67] They are constantly increased after a transfusion.[67] The increase is either

relative or absolute. Thus with 12% monocytes and a total count of 5,000, the absolute number will be 600 (normal maximum 700 - Wiseman[91]) - relative monocytosis - while with 12% monocytes and a total count of 9,000 the absolute number is 1,080 - absolute monocytosis. Some of the monocytes are distinctly larger than the largest normal cell and these often show cytoplasmic vacuoles and engulfed red cells and even neutrophils and lymphocytes in their cytoplasm.

The lymphocytes have no noteworthy numerical or histological characters. Their percentage and absolute numbers fluctuate in the inverse ratio to those of the neutrophils and monocytes. Any lymphocytosis noted is always relative to the diminished number of neutrophils.

Eosinophils and basophils are usually absent. Basophils have hardly ever been recorded in S.B.E. (Blumer[6]).

The red cells, haemoglobin and colour index show characteristically a microcytic hypochromic anaemia. The colour index is consistently below unity. When first seen presenting with pyrexia (no embolic phenomena and no splenomegaly) there is often little or no anaemia. Sooner or later, however, a moderate anaemia is discovered, e.g. 50% haemoglobin and 3.0 million red cells. The anaemia remains almost stationary until the end when it usually increases and may become severe, e.g. less than 2 million reds and less than 30% haemoglobin.

General Survey of the Film. The platelets show variations in size and diminution in numbers. The erythrocytes are microcytic and hypochromic.

3. Septicæmia

The classical peripheral blood response in septicæmia is high leucocytosis due to neutrophilia, the neutrophils showing marked left shift and widespread toxic granulation. (Kugel and Rosenthal[44]). In the streptococcal and staphylococcal forms total white cell figures may reach 40 or 50 thousand per cmm. or above with neutrophil percentages of over 90. In chronic meningococcæmia the total counts rarely exceed 30,000 cells per cmm. Campbell[11] records 30,600 white cells per cmm. with 88% neutrophils in the single case in which a blood count was made, while Kinsman and D'Alonzo[42] give 25,000 as the maximum count in their cases with neutrophil percentages ranging from 80 to 96. When the causal organism is a hæmolytic coccus there is a rapidly developing hæmolytic anæmia, i.e. an anæmia with a normal colour index, the stained smear showing nucleated red cells, polychromasia and punctate basophilia. The urine gives positive tests for urobilin.

4. Chronic Fibrocaseous Pulmonary Tuberculosis

Active febrile cases of chronic phthisis present one or other of the following leucocytic patterns:- (i) A normal total and differential count. This is the usual finding in early cases. (ii) A total count within normal limits and a differential formula showing a relative monocytosis (over 10%) with normal neutrophil and lymphocyte figures. (iii) Moderate leucocytosis (12,000 to 16,000 cells per cmm.)

due to neutrophilia (75 to 80%) the neutrophils showing a moderate left shift, (20 to 30% non-filamented forms) relative lymphopœnia, monocytes within normal range and no eosinophils. (iv) Moderate leucocytosis with neutrophil and lymphocyte percentages about equal and with normal monocyte values. The red cells and hæmoglobin either show no departure from the normal in early febrile cases, or there is a moderate microcytic hypochromic anæmia. The erythrocyte sedimentation rate is characteristically raised, the rise persisting after the subsidence of the pyrexia. Exceptionally, however, the E.S.R. may be normal in the presence of active disease.

5. Tuberculosis of the Mediastinal Lymph Glands

No detailed studies could be found in the literature of the peripheral blood response in mediastinal tuberculosis.

6. Tuberculous Meningitis

No detailed studies of the peripheral blood in tuberculous meningitis are available. All that can be culled from the few references in the literature is that the prevailing white cell response is a polymorphonuclear leucocytosis. According to Ewing[22] "in 5 of the 7 cases reported by Cabot there was a distinct leucocytosis, the counts ranging between 14,700 to 34,300 cells per cmm."

7. Enteric Fever

The White Cells. Leucopœnia is the characteristic finding in the enteric fevers. The reduction in the total count is due to a marked diminution in the absolute number of the neutrophils, that is to say, there is an outspoken neutropœnia. The neutrophils exhibit a sharp increase in the non-filamented forms as well as widespread toxic granulation affecting both the segmented and non-segmented forms. (Kugel and Rosenthal[44]). The lymphocytes show a relative, never an absolute, increase in their numbers. Eosinophils are usually completely absent.

This leucocytic pattern may be found 3 or 4 days after the patient has taken to bed. On the other hand, in children under 5 years of age and in adults, when the disease is accompanied by symptoms of an upper respiratory infection, the neutropœnia may be replaced by a neutrophil leucocytosis during the first week of the illness. The neutrophils are deviated to the left and show toxic granulation, while eosinophils are conspicuously absent. But whatever the count turns out to be in the first week, the characteristic white cell pattern described in the opening paragraph is almost universally found in the second week of the illness, persisting, in the absence of complications such as perforation or bronchopneumonia, throughout the rest of the febrile period till defervescence. After that the count gradually returns to normal.

The Red Cells and Haemoglobin. A microcytic hypochromic anæmia accompanies the course of the enteric fevers. It is slowly but steadily progressive so that by the time the defervescent stage is reached, the haemoglobin has usually dropped to figures in the vicinity of 60% and the erythrocytes to about 3.0 million per cmm. or less.

A marked thrombocytopoenia usually accompanies the entire febrile stage of the disease followed by a sharp rise of the platelets to normal levels during convalescence.

8. Tabes Mesenterica

No reports could be found in the literature on the serial haemogram in proved cases of tabes mesenterica. From the few isolated blood counts available it appears that the pyrexia of tabes mesenterica may be accompanied either by a neutrophil leucocytosis (Allen[1]) or by a normal total and differential white cell count. (Madding and Masson[52]). Allen finds a leucocytosis but makes no reference to the differential count, while in Madding and Masson's case which showed a normal total count, "smears for special haematologic study ... showed toxic polymorphonuclear leucocytes with a slight shift to the left." Since it is not known which of these two is the commoner or whether repetition of the blood count would yield a more characteristic haemogram, such as for example a significant change in the monocyte figures, no attempt will be made to place tabes mesenterica in the haematological classification.

9. Brucellosis

Total Leucocytes. The total white cell count is either frankly leucopoenic, within normal range or slightly elevated, the elevation being rarely above 13,000 cells per cmm. Leucopoenia is usually found in acutely ill patients while normal or slightly raised counts characterize the less acute stage. In the series of 271 cases studied by Calder and his associates[10] the vast majority had counts below 9,000 per cmm., only 30 showing counts above that figure, and these were almost all below 13,000. In summary these cases showed normal counts in half of the cases, leucopoenia in 1/3 cases, and mild leucocytosis in 1/6 of the cases.

The Differential Count. (a) "The neutrophils are almost invariably reduced both in percentages and absolute numbers." (Calder et al.[10]). The percentage of non-filamented forms is largely within normal range. It is rarely above 8% and more rarely still above 15%. This contrasts with typhoid where the percentage of non-filamented forms is markedly raised (marked left shift). (b) The lymphocytes. Active lymphocytosis is a striking feature as evidenced by an increased absolute number and by the lymphocytic left shift. The percentage figures for lymphocytes are universally raised above the normal maximum of 35 and in the vast bulk of cases the lymphocytosis is absolute. Thus in the series studied by Calder et al.[10] 2/3 of the cases had normal or increased total counts and since the percentage of

lymphocytes was invariably raised, the lymphocytosis was absolute in 2/3 of the cases and relative in the remaining 1/3. In addition, the lymphocytes show a distinct left shift according to Wiseman's criteria of the age of lymphocytes.[92] In 4/5 of Calder's series the young forms (deeply basophilic cytoplasm and no azur granules) exceeded very materially Wiseman's normal maximum of 100 of these young cells per cmm. The immature lymphocytes frequently show nucleoli. Another feature of the series was the preponderance of large lymphocytes over small ones. (c) The monocytes. The percentage and absolute figures are largely within normal range. In only 16% of Calder's series were the monocytes raised above the normal maximum of 700 cells per cmm. They exhibit no structural deviation from the normal. (d) Eosinophils are never absent. In Calder's series approximately 20% of the cases showed over 4% eosinophils. An unusual proportion of these were non-filamented. (e) Basophils. 10% of the cases in Calder's series showed basophils in excess of 1%, the maximum percentage being 3. (f) Other cells. Concerning these, Calder and his associates[10] state: "In slightly more than 1/3 of our cases plasma cells were observed - they accounted for from 1-3% of the total leucocytes. Mononuclear cells with relatively large amounts of cytoplasm were observed but differed from the cells of mononucleosis by the absence of vacuoles and the light blue cytoplasm characteristic of the mononucleosis cell. Nucleated reds are infrequent."

The Red Cells, Haemoglobin and Colour Index. It is generally stated

that a moderate non-progressive microcytic hypochromic anaemia accompanies brucellosis. Calder and his associates[10] have, however, demonstrated that the anaemia is distinctly macrocytic, mild and non-progressive. The erythrocyte counts are approximately 0.5 million below the normal minimum while the haemoglobin values are normal. This was verified by the estimation of the mean corpuscular volume which was greater than 92 cubic microns (normal 82-92 cubic microns[90]) and checked against the Price-Jones Curve. In Calder's[10] series only 6 cases showed a microcytic hypochromic anaemia. The colour index, though a poor guide to cell size, is usually above unity.

General Survey of the Film. The red cells are on the whole larger than normal with minor variations in size, shape and staining characters. Hypochromia and microcytosis are distinctly rare. Now and again the monocytes show phagocytosis of red cells.

These numerical and morphological changes in the peripheral blood of brucellosis constitute a haematological pattern of real diagnostic value, and as Calder and his co-workers declare "form a fundamental part of the disease and are duplicated in their entirety by no other known disease."

10. Acute Miliary Tuberculosis

The White Cells. The value of serial haemography in the diagnosis of obscure fever is nowhere better illustrated than in acute miliary

tuberculosis. Chapman and Whorton,[13] in one of the few reports in the literature on the peripheral blood in acute miliary tuberculosis, rightly declare that "serial examinations of the red and white cells appear to be of considerable diagnostic assistance but isolated examinations are probably misleading as often as they are helpful."

The characteristic white cell pattern is leucopœnia with relative neutrophilia, the neutrophils showing marked left shift. The leucopœnia may be extreme with counts of 1,000 or even lower. The lowest count in Chapman and Whorton's[13] series of 49 hæmatologically studied cases was 1,600 cells per cmm. Neutrophil percentages of over 80 are the rule with 96% as the top figure.[13] In most cases the immature (unsegmented) forms constitute well over 25% of the neutrophils. The non-filamented cells not infrequently outnumber the mature forms. Widespread toxic granulation affecting the mature and non-filamented neutrophils is a striking feature of the stained film. (Kugel and Rosenthal[44]).

It is necessary to remember that this characteristic white cell ensemble - leucopœnia with relative neutrophilia - is not necessarily maintained throughout the course of the disease; the total and differential counts may vary from time to time in the same patient. In Chapman and Whorton's blood studies in 49 pure cases of acute miliary tuberculosis, i.e. without chronic phthisis "there was leucopœnia (a total leucocyte count of less than 5,000) at some point

during the hospital course in 24 of the cases (49%) and in 16 cases (33%) the total leucocyte count was within normal range."[13] In other words in over 80% of the cases the total count showed either an absolute leucopoenia or a relative leucopoenia in relation to the temperature. Some of the counts may show a leucocytosis of 20,000 cells per cmm.

The differential formula, like the total leucocyte count, may exhibit departures from the characteristic relative neutrophilia. Thus, very exceptionally, there may be a temporary increase in the lymphocyte percentage with a normal or slightly reduced percentage of neutrophils as occurred in 4 of Chapman and Whorton's cases. But repetition of the count will hardly ever fail to demonstrate the characteristic trend towards leucopoenia with relative neutrocytosis, neutrophilic left shift and widespread toxic granulation. This characteristic blood pattern may persist for "two weeks or more, the longest period of leucopoenia being twenty weeks." (Chapman and Whorton[13]). Another point of importance is that persistent monocytosis never occurs in acute miliary tuberculosis. In Chapman and Whorton's[13] series "persistent monocytosis was not present in any case."

The Red Cells and Haemoglobin. Anæmia is the rule. It is usually normochromic, sometimes microcytic hypochromic and almost always moderate in degree. The haemoglobin range is stated to be between 65 and 85% (Sahli) and the erythrocyte range between 3.5 and 4.5 million per cmm. Severe anæmias are rarely met with in acute miliary tuberculosis.

11. Chronic Miliary Tuberculosis

The blood picture in chronic miliary tuberculosis has not hitherto been seriously studied. In the few instances where blood counts were made total and differential leucocyte values were within normal range and there was no significant anaemia. The erythrocyte sedimentation rate is raised.

12. Primary Atypical Pneumonia

The Total Leucocyte Count. The total leucocyte count during the febrile period is either within normal range or frankly leucopoenic. When the count is normal it is rarely above 8,000 cells per cmm. In Maxfield's[55] series of 63 cases "82% had a white blood count of less than 8,000." The count occasionally rises to 12,000 (Maxfield) but in general "an initial leucocyte count of 12,000 or higher was found to be due to ... previous vomiting or secondary infection of the sinuses, ears, pharynx." (Schmitz[76]). When there is leucopoenia the white cells range between 2,500 and 4,500 cells per cmm. with some of the counts, among the sickest patients, dropping to 1,800 (Cass[12]). An important diagnostic point showing the value of the serial haemogram is the observation that during convalescence the total white cell count rises to between 10,000 and 22,000 cells per cmm. This rise which is usually due to an increase of the lymphocytes (Grossman[30]) is regarded as a good sign. (Schmitz[76]). In the absence of facilities for serial radiography of the chest this

rise may be taken as evidence of resolution of the lesion. The leucocyte count begins to rise on the second or third day before the temperature begins to drop, reaching its peak two or three days after the temperature has reached normal levels.

The Differential Formula. "The neutrophils vary from 40 to 80%." (Maxfield[55]). When the count is frankly leucopoenic as in Cass'[12] series, the neutrophils range between 80 and 90% (relative neutrophilia). "Toxic granules may be seen in the cells and there is usually a shift to the left." (Schmitz[76]). "The mononuclear leucocytes (monocytes) were 8% or above in 38% of the cases." (Maxfield[55]). There is no anæmia.

13. Lymphocytic Choriomeningitis

The peripheral blood picture in the pre-meningeal or prodromal phase is characterized by "a definite leucopoenia with granulocytopoenia, relative lymphocytosis and relative monocytosis at first and after a few days an eosinophilia of 5 to 8% may appear." (Farmer and Janeway[24]). With the advent of meningeal irritation the leucopoenia of the prodromal period gives place to a normal total and a normal differential in the vast majority of cases. Occasionally the total leucocyte count rises to 20,000 cells per cmm. due to neutrophilia. There is no anæmia. "On the contrary there is often an increase in the red cell count of 1 to 2 million cells per cmm. The sedimentation rate is normal." (Farmer and Janeway[24]).

14-17. The Rickettsial Diseases

The white cell count in the rickettsial diseases is either frankly leucopoenic or within normal limits. Frank leucopoenia is said to be more common in flea-borne than in louse-borne typhus. (Dyer[20]). A total count above the normal maximum of 10,000 cells per cmm. is exceptional, and when this occurs the figure of 15,000 cells per cmm. is rarely, if ever, exceeded in uncomplicated cases.[28,20] In a word, leucocytosis if present is slight in uncomplicated cases.

The differential formula may be normal or show a relative or absolute increase of the mononuclear cells (lymphocytes and monocytes) with left shift of the neutrophils. In African tick-bite fever and in epidemic typhus relative monocytosis is a most striking feature. (Kugelmass[45]). The eosinophils tend to disappear in the serial hæmogram "but not quite so rapidly and uniformly as in typhoid fever." (Gradwohl[28]). According to Schilling the thick drop preparation in epidemic typhus gives a "gay colourful" picture owing to the presence of many plasma cells and Türk irritation forms." (Gradwohl[28]).

In regard to the red cells and hæmoglobin "most authorities speak of a marked decline of the erythrocytes in typhus accompanied by a hæmoglobin drop" (Gradwohl[28]) "leading to the development of a severe normocytic anæmia with nucleated erythrocytes, anisocytosis and poikilocytosis." (Kugelmass[45]). In the remaining members of the

rickettsial diseases no anaemia has been recorded.

18. Secondary Syphilis

The blood count in secondary syphilis reveals a leucocytosis due to absolute lymphocytosis. "Leucocytes usually number from 12,000 to 20,000 cells per cmm. ... and the increase is brought about by an absolute lymphocytosis amounting to some 50% of the total count." (Whitby and Britton[85]). The lymphocytes are all of the normal small variety. Occasionally the white cell picture is characterized by an outspoken eosinophilia. (Spangler[80]). Anaemia is a feature of secondary syphilis. It is usually normocytic normochromic and of moderate degree, but it may be microcytic or macrocytic. The anaemia, whatever the type, is sometimes progressive and severe.

19. Relapsing Fever

During the pyrexial bouts both the total and differential white cell counts are usually within normal range. Five of Taft and Pike's[83] eleven cases had normal total and differential counts. Occasionally, however, there is a mild leucocytosis of up to 15,000 cells per cmm. due to neutrophilia with the neutrophil percentage in the vicinity of 75%. The noteworthy feature of the blood picture of relapsing fever is the outspoken leucopoenia which characterizes the afebrile intervals. Total counts of 3,000 cells per cmm. or less are a common finding during remissions.

"Anaemia is a constant feature in persistent infections, but it is not severe ... Blood platelets are almost invariably reduced to figures of 100,000 per cmm. or even less." (Whitby and Britton[85]). The anæmia is usually normocytic.

20. Malaria

Examination of the blood is best made during the first 6 hours following a paroxysm. It is at this time that the characteristic blood changes of malaria are best seen. Moreover, the parasites are most numerous in the peripheral blood at this time.

The White Cells. In all the four forms of malaria (benign tertian, ovale tertian, quartan and malignant tertian) the white cell count is characteristically leucopœnic, 3,000 to 4,000 cells per cmm. being the usual finding when the blood is examined within 6 hours after the temperature has dropped to normal. The temperature typically reaches fastigial levels at 6 a.m., 10 a.m., or 2 p.m., being normal or subnormal between 6 and 10 p.m. During the paroxysm at the height of the fever, the total count is temporarily raised, usually to 11,000 and rarely above 15,000 cells per cmm. but it may go up to much higher levels, e.g. 46,000. (Most and Meleney[60]).

The differential formula reveals a relative monocyte increase to between 15 and 20%. The lymphocytes and neutrophils are within normal range, the latter exhibiting marked left shift, the shift cells

consisting solely of juvenile non-filamented forms. In malignant tertian (falciparum or subtertian) malaria the monocytes and neutrophils contain numerous coarse yellow or black granules (malarial pigment). They represent the phagocytosed debris of red cells and parasites, are best seen in thick smear preparations and are pathognomonic of falciparum malaria even if parasites are undemonstrable. Special staining for toxic granulation shows the presence of coarse blue dots (toxic granules) in the cytoplasm of the adults and juvenile neutrophils - evidence of the action of the malarial toxin on the bone marrow.

The Red Cells and Haemoglobin. A haemolytic anaemia is the rule in all malarial infections (except the ovale tertian forms - Manson-Bahr[54]). The red cells are reduced in numbers pari passu with the haemoglobin giving a normocytic anaemia and the stained film shows nucleated red cells and punctate basophilia. The haemolytic process is also reflected in the skin which is icteric and in the urine which contains urobilinogen. Urobilinogen should be looked for at the height of the fever for it may disappear directly the temperature drops.

21. Visceral Leishmaniasis

The conspicuous and characteristic haematological finding in kala-azar is the outspoken leucopoenia. Total counts of 3,000 white cells per cmm. are repeatedly registered in the serial haemogram, and

counts of 1,000 and even 500 cells per cmm. have been recorded in the presence of fever. The reduction affects the neutrophils and eosinophils only, the lymphocytes showing a relative increase and the monocytes both a relative and, often also, an absolute increase. Monocytosis is a feature, 15 to 20% monocytes being a common finding and percentages of 40 and over are not unusual. The eosinophils disappear. The red cell-haemoglobin ensemble reveals an anaemia which is largely normocytic, but sometimes microcytic hypochromic with no special change in the morphology of the red cells. It is usually only moderate in degree even in advanced cases. The anaemia, it may be pointed out, is never haemolytic (compare malaria) and not marked or progressive (compare leukaemia). The platelets are normal in shape, size and numbers. Owing to the intense granulocytopœnia kala-azar subjects are liable to infections, particularly pneumonia and buccopharyngeal and intestinal ulceration, (mucosanguineous diarrhoea) any or all of which may finally come to dominate the clinical picture.

22-30 Deep-seated Abscess

The classical peripheral blood findings associated with deep-seated suppuration are as follows:- (a) Neutrophil leucocytosis. (b) The neutrophils are uniformly deviated to the left. (c) Widespread toxic granulation. (d) Eosinophils are usually either persistently absent or distinctly diminished below the normal minimum of 150 per cmm.

(Schilling.[75] (e) Lymphocytes and monocytes are reduced below their normal minimum relative and absolute values. (f) Normocytic anæmia, the severity and progress of which are dependent on the virulence of the infecting organism and the duration of the infection. The anæmia is resistant to all forms of medication, responding only after the abscess has been evacuated and drained, and then only very slowly. (g) Thrombocytosis. On the stained film this is evidenced by the abundance of the platelets and their abnormally large size.

The leucocytic changes may vary quantitatively in the serial haemogram of the same conditions as well as in the various anatomical situations of the abscess, but qualitatively they constitute the classical haematological ensemble of deep-seated suppuration.

The magnitude of the count is of little value as an index to the nature of the infecting organism. In regard to the degree of leucocytosis all that can be said that is of practical value is that a neutrophil leucocytosis of 30,000 cells per cmm. or higher when found in an obscure fever may be considered as strongly suggestive of the existence of deep-seated pus somewhere in the body. Such a finding coupled with a history of an antecedent condition of which deep-seated abscess is a recognized complication, (v.p109) is almost diagnostic.

When the leucocytosis is not impressive or the total count is within normal range, a persistent and distinct rise in the

non-filamented neutrophils in the serial haemogram together with the presence of toxic granulation, constitutes highly significant evidence in favour of deep-seated suppuration.

31. Carcinoma of the Stomach

The blood findings may be of interest in the differentiation of malignant disease of the stomach from other causes of prolonged cryptic fever. Oppenheim and his co-workers[65] in a study of 122 cases of adenocarcinoma of the stomach reached the following conclusions concerning the red cell and haemoglobin pattern:- (i) The anæmia may be micro-, macro- or normocytic using the mean corpuscular volume (normal 82 to 92 cubic microns[90]) not the colour index as the criterion of cell size; (ii) When the anæmia is macro- or normocytic it is always normochromic, while, when the anaemia is microcytic it is normochromic in about 75% and hypochromic in about 25% of the cases, using the mean corpuscular hæmoglobin concentration as the criterion (normal 32-36%[90]). The conclusion reached, therefore, is that, whatever the cell size, the anaemia of gastric carcinoma is almost universally normochromic and never hyperchromic. These workers further indicate that at most 5% of patients with cancer of the stomach have a pernicious anæmia picture covering all the criteria for the diagnosis of Addisonian anaemia. These are presumably the examples of the now well known pernicious anaemia - gastric cancer sequence reviewed by Rigler et al.[73] who found an incidence of 12.3% of carcinoma of the

stomach in 293 cases of Addisonian pernicious anæmia.

The white cell distribution accompanying the anaemia of gastric carcinoma is as follows:- (i) The total leucocyte count in slowly growing tumours is slightly raised, rarely above 15,000 cells per cmm., due to an increase in the neutrophils to between 70 and 80%. (ii) The neutrophils exhibit a moderate to marked left shift - 15 to 40% non-filamented forms - and toxic cytoplasmic changes (Harkins[34]). (iii) The lymphocytes show the usual reduction reciprocal to the neutrophil increase, and the monocytes are normal. (iv) Eosinophils may be absent, normal or increased. On the other hand, the white cell picture in slowly growing tumour may remain essentially normal for weeks or months on end. In rapidly growing gastric carcinomata, the total count may be exceptionally high particularly when there is bone metastasis, when the blood picture may suggest myelogenous leukaemia.

32. Lymphosarcoma of the Mediastinal Glands

We are not here concerned with the blood findings of those examples of lymphosarcoma of the mediastinum which do not present with cryptic fever. These examples usually show no detectable changes in the peripheral blood, excepting perhaps a secondary anæmia." (Wiseman[91]). But when lymphosarcoma presents with cryptic fever the peripheral blood is almost universally characterized by a conspicuous lymphocytic leucocytosis reminiscent of chronic lymphatic leukaemia, the lymphocytes

being almost entirely of the small adult variety. This accession of small lymphocytes in the peripheral blood is due to "the neoplastic cells breaking loose into the blood stream." (Wiseman[91]). These cells are cytologically "indistinguishable from normal small lymphocytes." (Ogilvie[64]).

33. Hypernephroma

The only haematological finding of interest in Ljunggren's[49] case report is the tendency to a low normal or leucopœnic total white cell count. The white cells varied between 3,000 and 5,600 per cmm. It is interesting to speculate whether a tendency to leucopœnia is a specific blood finding in pyrexia due to the presence of a necrotic tumour mass without superimposed infection, without gross bleeding and without metastasis to bone. For these were the autopsy findings in Ljunggren's case. It is only by routine haemography in all cases of obscure fever that we can hope to establish a blood pattern in uncomplicated malignant disease. There is no record of the differential count in Ljunggren's[49] case. We are left to speculate, therefore, concerning the cells which were mainly affected in the leucopœnia, whether they were the polymorphonuclears or the mononuclear elements. The erythrocyte sedimentation rate was persistently raised to between 59 and 96 mm. at 1 hour. (Westergren).

34. Infectious Mononucleosis

The total leucocyte count lies, in the majority of instances, between 10,000 and 20,000 cells per cmm. This usually prevails from the onset to the termination of the pyrexia, and often for many months thereafter. Exceptionally a high leucocytosis with counts up to 63,000 cells per cmm. due to neutrophilia may be a feature either during the first week or may dominate the blood picture from the beginning to the end of the pyrexial period. (Wintrobe[90]).

In the differential formula two outstanding features prevail which, taken together, are pathognomonic of Infectious Mononucleosis. (i) A preponderance of mononuclear cells which make up at least 60% and often as much as 95% of the leucocytes. The normal maximum percentage of mononuclear elements (lymphocytes and monocytes) does not exceed 45 after the age of 4 years. "This mononuclear preponderance begins on the fourth or fifth day and attains its peak by the seventh or tenth day." (Wintrobe[90]). Sometimes, however, as Contratto[14] points out, "there is a delay of days or even weeks before the haematologic changes are conclusive enough to permit an accurate diagnosis." (ii) The second dominant feature of the stained film is the striking picture presented by the characteristically pleomorphic nature of the mononuclear cells. These cells are of different shapes and sizes, their nuclei are of diverse morphology and their cytoplasm staining varying shades of blue. This multiform

mononuclear morphology, together with the preponderance of mononuclear cells, constitutes a most impressive feature of the general aspect of the stained film from which a diagnosis of infectious mononucleosis can be made with reasonable assurance on haematological grounds alone. "The variety of the mononuclear cells is the predominating feature." (Tidy[84]). The practical point about these cells is that they are difficult to classify, i.e. they do not answer to the description of lymphocytes, monocytes or any of the leucocyte precursors, and that some have a vacuolated foamy cytoplasm. The characteristic mononuclear picture continues for a long time, it may be for months, after the subsidence of the fever, the patient appearing perfectly well. Finally, after a varying interval the blood picture returns to normal.

The neutrophils are morphologically normal and their percentage and absolute figures are inversely proportional to those of the mononuclear cells. There is no conspicuous increase in the non-filamented forms when the blood picture is of the classical type. In the exceptional cases mentioned, with neutrophilia, the polymorphs exhibit varying degrees of left shift. Eosinophils are usually absent during the fever, returning sometimes in increased numbers (e.g. 15%) during convalescence. This is a point worth remembering, for should the first blood count be done during convalescence, the antecedent pyrexia may be confused with the obscure fevers of the eosinophilic group. (Table 2 pages 83 & 84). An increase in the basophils up to 3% is sometimes found.

The erythrocytes, platelets, haemoglobin values and sternal marrow are in the vast majority of cases normal. Read and Helwig,[69] however, in a study of 30 cases of infectious mononucleosis all with positive Paul-Bunnell reactions found 3 cases with an aplastic type of anaemia with persistent leucopoenia, relative mononucleosis with mononuclear pleomorphism, petechial haemorrhages, anaemia and thrombocytopoenia. Serial blood counts, however, showed a gradual return of the blood picture to normal, demonstrating the paramount importance of the serial haemogram.

35. Infectious Lymphocytosis

The total white cell count in Smith's[77] cases in children was essentially normal for the age group, namely between 8,000 and 13,000 cells per cmm. In Duncan's[19] case I, a young adult aged 20 who ran a temperature for a month, the total count varied from normal through mild to marked leucocytosis, the lowest figure recorded being 6,400, the highest 28,000 cells per cmm. The differential formula reveals, both in children and adults, a marked preponderance of normal lymphocytes almost all of the small variety with a small percentage (rarely above 5%) of large ones. The highest recorded lymphocyte percentage in Smith's[77] series in children is 89% and in Duncan's[19] case 84% at the commencement, 77% after a fortnight of pyrexia and 41% round the defervescence. All the examples in Smith's[77] patients show

lymphocytes in excess of the top figure for the age group, i.e. above 55%. Serial counts taken during the course of the pyrexia demonstrate fluctuations both in the total and differential values. This is well illustrated in Duncan's[19] case. The neutrophils are correspondingly diminished. They are largely normal adults with a few non-filamented forms rarely exceeding 8%. The monocytes and eosinophils are numerically and morphologically normal. Occasionally a slight anaemia develops, usually normocytic, but in the main anaemia is absent throughout. As in the acute form the course is uneventful, ending in complete clinical and haematological recovery. No fatalities have been reported.

36. Acute Aleukæmic Leukæmia

In aleukaemic leukæmia "there may be no alterations whatever in the cellular elements of the blood." (Wiseman[91]). Nevertheless, the blood picture is still of very considerable assistance despite the absence of the pathognomonic immature leucocyte precursors, showing as it usually does the suggestive ensemble - leucopœnia or normal total white cell count with relative mononucleosis, thrombocytopœnia, rapidly progressive anaemia with numerous nucleated reds and little, if any, inequality in size and shape of the erythrocytes. The diagnosis may, however, require confirmation by sternal puncture. (v.p 28).

37. Hodgkin's Disease

Wiseman[91] in his paper on "The Blood Pictures in the Primary Diseases of the Lymphatic System," says: "The literature clearly indicates that there is no agreement among haematologists concerning the character of the blood picture in Hodgkin's Disease. Most observers feel that there are no typical changes; a few have indicated that the haematological criteria are quite definite ... These divergencies are due to a large extent to inaccurate observations ... Personal experience has convinced us that dependable blood examinations are beyond the capacity of the average laboratory technician ... For instance careful discrimination between lymphocytes and monocytes has not always been clearly evident ... the most exacting attention of the skilled haematologist is required ... Furthermore ... the diagnosis of Hodgkin's Disease has not always been controlled by adequate histological evidence." Wiseman[91] studied 31 histologically verified cases of Hodgkin's Disease from 1931 to 1936. He himself made all the blood studies. An average of 4 counts were made per patient and the conclusion reached was that "there are in the vast majority of cases quite characteristic changes in the blood" in Hodgkin's Disease.

Most of the cases with deep node involvement and pyrexia as an outstanding feature show either a normal or low total count. 24 of Wiseman's cases had total counts of 10,000 or below; the rest had a total count up to 20,000 cells per cmm. Those with over 10,000 were

far advanced with marked evidence of abdominal or mediastinal or peripheral node involvement.

The differential leucocyte count, like the total white cell count, may remain persistently normal but the most constant finding is an absolute lymphocytopoenia, absolute neutrophilia with absolute monocytosis. The following is an extract from Wiseman's paper:- "About 9/10 of the cases show absolute lymphocyte counts below the normal minimum of 1,500 lymphocytes per cmm. We have had the experience of searching a film for 15 minutes in proved cases of Hodgkin's Disease without encountering a single lymphocyte. We have not encountered a single case in which the number of lymphocytes has exceeded the normal." Wiseman declares that "absolute lymphocytosis excludes Hodgkin's Disease in any shape or form." The lymphocytes are largely mature, i.e. do not show young forms in excess of 100 per cmm. Nearly 2/3 of cases (i.e. 19 out of 31) had monocytes in excess of the normal maximum of 700 per cmm. Absolute lymphocytopoenia with co-incident neutrophilia and absolute monocytosis must, therefore, be regarded as an important diagnostic combination. There is a distinct tendency to absolute neutrophilia which is especially in evidence in primary affections of the deep glands. Absolute values of the neutrophils above the normal maximum of 8,000 cells per cmm. were found in about 14 out of the 31 cases studied (i.e. 45%). Cases showing marked neutropoenia probably reflect extensive marrow involvement which is sometimes a feature of the disease. The neutrophils, furthermore, show conspicuous left shift, the shift

cells consisting of non-filamented forms, blast cells being rare and when present suggest marrow involvement. The neutrophil left shift, which is a feature of Hodgkin's Disease irrespective of the total white cell and total neutrophil counts, is reminiscent of an infection, but unlike infection these cells show no toxic cytoplasmic changes. (Meranze, Mendell and Meranze[57]). The pyrexia of Hodgkin's Disease is further differentiated from the neutrophilia of infection by the presence of eosinophils in the majority of cases, eosinophils being classically absent or distinctly diminished in their absolute numbers during the course of an infection. (Schilling[75]). Eosinophils were almost always found present in Wiseman's series in association with neutrophilia. The absolute figures for the eosinophils during the Pel-Ebstein bouts are rarely below 200 per cmm., the normal range being 150 to 400. In summary, the combination absolute neutrocytosis with neutrophil left shift but without toxic granulation plus absolute monocytosis and eosinophils in normal absolute numbers is distinctly against infection on the one hand and strongly suggestive of Hodgkin's Disease on the other.

Eosinophilia, absolute or relative, is distinctly rare. At least 2/3 of the cases show no distinct elevation of the absolute eosinophil values above the normal maximum of 400 of these cells per cmm. Nevertheless, Wiseman says "an absolute eosinophilia is present often enough to constitute a valuable diagnostic sign when considered in

association with the other clinical and haematological features." According to Wintrobe[90] eosinophilia occurs in about 20% of cases. Eosinophilia is particularly rare in the early stages with which we are specially concerned here. In the later stages, with conspicuous peripheral adenopathy, values as high as 90% with markedly raised total white cell counts (50,000 to 100,000 per cmm.) have been recorded. (Wintrobe[90]). The eosinophils often contain very large granules. The basophils are almost always unchanged in number.

The red cells, haemoglobin and platelets. "A secondary anaemia of the haemoglobin type (i.e. hypochromic microcytic) is an almost constant feature ... It is mildly progressive but never severe in the early silent stages of Hodgkin's pyrexia. The data on the platelets are inadequate for a careful analysis."[91]

38. Filariasis Nocturna

Primary filarial fever (v.p 31) is characterized by an outspoken eosinophilia ranging between 9 and 36% (Hodge et al.[36] and Saphir[74]). It is particularly noteworthy that the incidence of eosinophilia is greater in those cases which present without localizing signs. (Hodge et al.[36]). The total leucocyte count is usually at the lower limit of normal. The average total count in the series studied by Hodge and his co-workers lay between 5,000 and 8,000 cells per cmm. and the distribution of the other white cells in the differential count was within normal range. There is no record of anaemia accompanying filarial fever.

39. Schistosomiasis (Anaphylactoid Stage)

The peripheral blood reveals a normal total white cell count, usually round 8,000 per cmm. and an intense eosinophilia, usually between 50 and 60%. The neutrophils are correspondingly reduced, the lymphocytes and monocytes being unaffected. There is no anæmia.

Molina and Pons[58] in their blood studies of a series of 20 cases of schistosomiasis mansoni, had only one case in the toxæmic stage which they subjected to a full haematological investigation. The routine blood count was as follows:- Total leucocytes 8,850 per cmm. Neutrophils 15% (filamented 4%, non-filamented 11%). Lymphocytes 23.5%. Monocytes 2.0%. Eosinophils 59.5% (absolute number 5,266 per cmm.)

40. Trichiniasis

The blood picture is almost invariably characterized by an impressive relative and absolute eosinophilia. The total leucocytes are usually either within normal range or only slightly raised. The eosinophils are usually between 10 and 35%, but may reach 60% and over. In Lehrfeld and Breisacher's[46] case the serial haemogram showed a total white cell count between 10,000 and 12,800 per cmm. with the eosinophils persistently raised to between 15 and 28%. Of the 11 cases described by Reifenstein et al.[71] there was an eosinophilia varying between 10 and 30%. It is, however, only fair to say that eosinophilia

is not present in 100% of cases. It is, nevertheless, sufficiently prevalent to be considered a valuable diagnostic criterion of the presence of the infestation. The importance of serial repetition of the blood count to pick up the eosinophils is demonstrated by Cabot's case in which there was no increase in the eosinophils until 10 days after the onset. Reifenstein's cases all showed eosinophilia early in the third week. There is no anæmia and the rest of the leucocytes vary in the inverse ratio to the eosinophils, sometimes the neutrophils at others the lymphocytes showing a reciprocal increase or diminution in the percentage values.

41. da Costa's Syndrome

No blood studies are available in the 30 cases studied by Friedman.[27] It is, however, more than likely that had serial haemograms been made they would have shown a consistently normal blood picture.

42. Periarteritis Nodosa

Total Leucocytes. A raised total white cell count is the rule in periarteritis nodosa. Normal figures are recorded very infrequently. It is usually over 15,000 cells per cmm. All the 8 cases described by Rackemann and Green[68] had a white cell count of 16,000 or over. In Grant's[29] cases, where a count is recorded, it is usually over 15,000. The leucocytosis in periarteritis nodosa exhibits wide variations in

degree both from case to case as well as in the serial readings of the same patient. It may reach 50,000 cells per cmm. or higher. (Lubowich and Hunt[50]). The differential count shows either an absolute neutrocytosis or an absolute eosinophilia. Absolute neutrophilia is said to be the more common finding. Grant[29] puts the incidence of absolute eosinophilia at 30%. Many observers, however, have shown that, if the isolated blood count is replaced by serial haemography, eosinophilia will be found to be of much more frequent occurrence. Haining and Kimball[32] recommend repeated white blood counts and differentials to pick up an eosinophilia which may otherwise be missed. "Practically all recent workers have emphasized the fact that, while not all cases of periarteritis nodosa show an eosinophilia, yet an eosinophilia is a highly significant diagnostic sign." (Lubowich and Hunt[50]). Even in the few examples where the total white count is within normal limits the eosinophil percentage is usually outspokenly raised.[50] Lubowich and Hunt's case which was well studied haematologically, clearly demonstrates the importance of repetition of the blood count. "The first count showed no abnormal rise in the eosinophils (13,400 cells with 2% eosinophils) which appeared in large numbers (e.g. 38,200 total white cells with 68% eosinophils) only after a considerable time following the onset of the illness but remained so till the very end." (Lubowich and Hunt[50]). In Rackemann and Green's[68] 8 cases the eosinophils were at least 25%. Until such time as further haematological studies have shown conclusively that the incidence of

eosinophilia is higher than that of neutrocytosis, it has been thought preferable in the meanwhile to include periarteritis nodosa with the obscure fevers accompanied by a polymorphonuclear leucocytosis.

The monocytes are normal, while the lymphocytes fluctuate in the inverse ratio to the neutrophils and eosinophils.
The red cells and haemoglobin are either normal throughout or show a moderate non-progressive microcytic hypochromic anaemia. In Lubowich and Hunt's case no anaemia was recorded throughout the 8 months course of the illness.

43. Acute Disseminated Lupus Erythematosus

Outspoken and persistent leucopoenia is of such frequent occurrence in acute disseminated lupus that it is justly regarded as an outstanding feature of the disease. The serial haemogram of the same patient shows total leucocyte counts repeatedly below 4,000 cells per cmm. with some of the figures as low as 1,000. (Blount and Barrett)[5]. The neutrophils show normal or slightly raised percentage figures and, generally, also left shift. Eosinophilia has never been encountered. Intercurrent infection replaces the leucopoenia by a neutrophil leucocytosis. Anaemia, absent in the early stages, develops as the disease progresses. It is almost invariably microcytic hypochromic and rarely severe, except terminally when the red cell count may drop rapidly to below a million. Thrombocytopoenia is a feature, especially

in the advanced stages when the platelet count may drop to 100,000 or less.

44. Chronic Subdural Hæmatoma in Infants

The blood picture is within normal range.

45. Chronic Nasopharyngitis

No detailed blood studies were attempted by O'Connor[63] in his 55 cases of chronic nasopharyngitis presenting with prolonged fever. To quote the author: "A moderate leucocytosis, 10,000 to 15,000 may be present, although the leucocyte count is not infrequently within normal range." When a leucocytosis is found the neutrophils show no toxic granulation. (Meranze et al.[57]).

46. Neurogenic Fever

A persistently normal blood picture presumably prevails in neurogenic fever but no haematological studies are recorded by the authors dealing with the subject. (v.p 36).

47. Pink Disease

The blood picture of Pink Disease has not received much attention. In the 2 cases quoted by Kinnier Wilson[87] there were

16,400 and 30,000 white cells per cmm. respectively. Nothing is said about the differential count. He remarks that erythrocythaemia may be a feature. If so, it is probably accounted for by the dehydration which follows the excessive sweating which is a feature of the disease.

48. Regional Ileocolitis

In Sprague's[81] case which was that of a European girl aet 15, the leucocyte count varied between 6,350 and 9,450 per cmm. with a normal differential. The haemoglobin was 70% (Sahli), erythrocytes 3.55 million per cmm. No significant changes were noted in the blood picture during the entire 6½ months period when pyrexia was the only outward manifestation of the disease. The E.S.R. was 30 mm. at 1 hour (Cutler).

49. Drug Fever

Three types of blood dyscrasias are found in Drug Fever:- Aplastic Anaemia, Haemolytic Anaemia and Granulocytopoenia.

Aplastic anaemia is a pan-cytopoenia, i.e. there is a reduction in the peripheral blood of all the formed elements produced by the bone marrow including the platelets. There is an associated relative lymphocytosis (70-90%). Clinically waxy pallor, purpura and bucco-pharyngeal ulceration are the salient features. This type of anaemia may accompany the pyrexia of gold, the organic arsenicals and dinitrophenol.

Haemolytic anæmia is normocytic with marked anisocytosis, polychromatophilia, spherocytosis, (Dameshek and Schwartz[16]) numerous nucleated red cells and abnormal rouleaux formation. There is polymorphonuclear leucocytosis with left shift, many of the shift cells being myelocytes and even myeloblasts. Thrombocytosis is a feature, the platelets being often of unusually large size. Clinically there is haemolytic icterus with dark stools, urobilinuria and, when haemolysis is extremely rapid, frank haemoglobinuria with haemoglobin casts in the centrifuged deposit. The temperature varies between 100 and 105°F with a disproportionate tachycardia. There is an associated spleno-hepatomegaly. Haemolytic anaemia as well as granulocytopoenia are the blood dyscrasias which accompany the pyrexia of the sulphonamide drugs, especially sulphanilamide and sulphapyridine.

Granulocytopoenia which is the blood dyscrasia of the drug fever due to sulphonamide medication, chrysotherapy and thiouracil is characterized by a rapid rise of the temperature to 105°F, the pulse rate running parallel with the temperature. The most outstanding clinical feature is the extreme prostration. Sore throat is the rule but occasionally in the early stages it is absent, and when this is so the physical examination is completely negative. The blood count is the clue to the diagnosis. The total white cells are invariably below 2,000 per cmm. and often below 1,000. On the stained film the leucocytes are conspicuously scanty and consist almost entirely of lymphocytes with a few monocytes. Neutrophils are either completely

absent, and when found at all they make up only about 5% or less of the differential formula. The erythrocytes are normal both in number and morphology and so are the platelets. There is no reduction of the hæmoglobin. Serum sickness is associated with an eosinophilia.

50. Bed Fever

The blood count and sedimentation rate are both persistently normal in Bed Fever. Since Bed Fever is only to be considered as a possible cause of prolonged low grade pyrexia after an infection "when the fever persists beyond what we have reason to expect should be its natural term" (Cabot[9]) it is necessary to make sure that the infective process has subsided before the diagnosis of Bed Fever is made. Reich and Reich[70] have shown that "a patient should not be regarded as entirely recovered from an infection until the lymphocytic formula has returned to normal." (v.p 88). The hæmatological criteria for the diagnosis of Bed Fever, therefore are as follows:- (i) Normal total white cell count. (ii) Normal neutrophil count without left shift and without toxic granulation. (iii) No lymphocytic left shift, i.e. the Y and M lymphocytes are within the normal range of 5 and 45% respectively. (iv) Normal sedimentation rate.

51. Spurious Fever

A persistently normal blood count and sedimentation rate serve to confirm the clinical suspicion of Spurious Fever.

(b) HAEMATOLOGICAL CLASSIFICATION OF THE OBSCURE FEVERS

From the foregoing blood studies it is possible to classify the obscure fevers listed in Table I pages 4 and 5 into 7 haematological groups based on the trend of the leucocytic pattern as revealed by serial haemography: 5 main groups and 2 sub-groups. (vide Table 2 pages 83 and 84). Seven of the obscure fevers (Group 6) still await detailed blood studies and are therefore, as yet, haematologically unclassifiable. It must be stressed that serial repetition of the blood count is necessary in order to pick up the characteristic white cell pattern upon which this classification is founded. Starting on the 7th day from the inception of the fever a complete routine blood count must be made on alternate days until one of the 7 leucocytic patterns has been identified. As a rule 6-8 haemograms will be needed. In addition to this, 2 complete blood counts, one on alternate days, should be made whenever the temperature drops and remains normal for 24 hours. Such a series of haemograms when made available for study will reflect the design of the peripheral blood response which characterizes each of the 44 haematologically classifiable conditions. The need for a repetition of the blood count after the subsidence of the temperature, has been indicated in the course of the haematological survey. The following 2 examples will serve to refresh the memory. In the febrile period of Primary Atypical Pneumonia the total white cell count is either normal

- or -

TABLE 2 HAEMATOLOGICAL CLASSIFICATION OF TH

GROUP I		GROUP 2	
Leucocytosis (More than 10,000 cells per cmm)		Leucopœnia (Less than 4,000 cells per cmm)	
(a)	(b)	(a)	(b)
Polymorphonuclear Leucocytosis (More than 8,000 P.M.N. per cmm)	Mononuclear Leucocytosis (More than 3,700 M.N.L. per cmm)	With Relative Neutrophilia (More than 70% P.M.N.)	With Relative Mononucleosis (More than 45% M.N.L.)
Typically in:	Typically in:	Typically in:	Typically in:
Rheumatic Fever	Brucellosis (1/6 of the cases - Calder et al)	Acute Miliary Tuberculosis (49% of cases - Chapman and Whorton)	Brucellosis (1/3 of the cases - Calde et al)
Septicæmia	Secondary Syphilis	Primary Atypical Pneumonia (Cass and Maxfield)	Enteric Fever
Chronic Phthisis	Lymphosarcoma of the Mediastinal Glands	Acute Disseminated Lupus Erythematosus	Lymphocytic Choriomeningitis
Deep-seated Suppuration	Infectious Mononucleosis		The Rickettsial Diseases
Carcinoma of the Stomach	Infectious Lymphocytosis(in adults)		Malaria
Hodgkin's Disease (45% of cases - Wiseman)	Atypically in:		Visceral Leishmaniasis
Periarteritis Nodosa	The Rickettsial Diseases (exceptionally)		Aleukæmic Leukæmi
Drug Fever with Hæmolytic Anæmia			Acute Disseminated Lupus Erythematosus
Atypically in:			Drug Fever with Aplastic Anæmia or with Granulocytopœnia
Subacute Bacterial Endocarditis			Atypically in:
Enteric Fever during the first week			Infectious Mononucleosis (with Aplastic Anæmia Read and Helwig)
Primary Atypical Pneumonia (occasionally - Maxfield)			
Relapsing Fever (occasionally)			
Infectious Mononucleosis (exceptionally - Wintrobe)			

DISEASES PRESENTING WITH OBSCURE FEVER

GROUP 3	GROUP 4	GROUP 5	GROUP 6
Eosinophilia (More than 400 Eosinophils per cmm)	**Normal Total with Abnormal Differential Leucocyte Count** *	**Normal Total and Normal Differential Leucocyte Count**	**Haematologically as yet Unclassifiable**
Typically in: Filariasis Schistosomiasis Trichiniasis **Atypically in:** Secondary Syphilis (exceptionally - Spangler) Hodgkin's Disease (20% of cases - Wintrobe) Periarteritis Nodosa (30% of cases - Grant)	**Typically in:** Subacute Bacterial Endocarditis Chronic Phthisis Brucellosis (½ the cases - Calder et al) Acute Miliary Tuberculosis (33% of cases - Chapman and Whorton) Primary Atypical Pneumonia The Rickettsial Diseases Carcinoma of the Stomach Infectious Lymphocytosis(in children) Acute Aleukaemic Leukaemia Hodgkin's Disease **Atypically in:** Deep-seated Suppuration Periarteritis Nodosa (very infrequently) * For the nature of the respective abnormalities of the differential formula see text	**Typically in:** Chronic Phthisis Primary Atypical Pneumonia (Maxfield) The Rickettsial Diseases Relapsing Fever Hodgkin's Disease da Costa's Syndrome Chronic Subdural Haematoma in Infants Neurogenic Fever Regional Ileocolitis Bed Fever Spurious Fever **Atypically in:** Carcinoma of the Stomach	Tuberculosis of the Mediastinal Lymph Glands Tuberculous Meningitis Tabes Mesenterica Chronic Miliary Tuberculosis Hypernephroma Chronic Naso-pharyngitis Pink Disease

or leucopoenic with the differential formula showing an absolute or relative neutrocytosis. During convalescence there is usually a lymphocytic leucocytosis. (vide p 55). In Relapsing Fever the total and differential counts are usually within normal range in relapse, with an outspoken leucopoenia in remission. (vide p 58).

The routine blood count should consist of the following items:- 1. The total leucocyte count. 2. The differential leucocyte count which includes the differentiation between filamented and non-filamented forms using Cooke and Ponder's[15] criteria. 3. The examination for toxic granulation of the neutrophils (Kugel and Rosenthal[44] and Meranze et al.[57]). 4. The general survey of the stained film. 5. The total erythrocyte count. 6. The estimation of the haemoglobin. 7. Calculation of the colour index.

Apart from certain exceptions which have been considered in section (a) e.g. Malaria, the best time of the day for the routine examination of the peripheral blood is at 6 p.m. At this time the temperature is usually at its height and the post-prandial leucocytosis has disappeared. The results obtained from capillary and venous blood are comparable.

The haematocrit and the other appurtenances employed in complete haematological studies are seldom, if ever, required in the blood studies in obscure fever.

In the haematological studies of a case of obscure fever the importance of the routine filament - non-filament neutrophil count and of the routine search for the presence of toxic granulation in these cells cannot be overestimated. Kugel and Rosenthal[44] stress the importance of these findings as follows: "Leucocytosis and polynucleosis may be absent in infectious conditions which are more or less severe. In such instances the ordinary blood examination may be insufficient or misleading, while attention to certain other details of the individual cell, such as nuclear and cytoplasmic changes, may indicate the presence of an underlying bacterial infection." Regarding the toxic cytoplasmic changes in the neutrophils Mendel et al.[56] point out that "with but few exceptions, all the studies recorded in the literature on leucocytic changes in infection deal with nuclear changes," and that "little attention has been devoted by contrast to the cytoplasmic alterations in neutrophils during disease states." Toxic granulation has the same significance as the neutrophil left shift and in a given case of obscure fever it indicates the same possibilities. Mendel and his collaborators[56] point out that toxic granulation as an index of the existence of infection is superior to the neutrophil left shift. "We noted in the course of our serial examinations" they state "that the degenerative cytoplasmic changes appeared earlier in the illness and persisted longer throughout the course than did the corresponding nuclear changes." Toxic granulation is not found in health.[44,90]

Speaking of the significance of the neutrophil left shift (an increase in the non-filamented forms above the normal maximum of 5% - Osgood[66]) Mendel and his associates[56] make the following statement: "The neutrophil left shift follows more closely the course of the infection ... than the total leucocyte count or the clinical impression. As infection progresses ... there is an increase in the band forms ... often unrelated to the magnitude of the total white count." In other words, even when the total leucocyte count is within normal limits, the co-existence of a neutrophil left shift indicates a coccal or bacillary infection and "a steady rise in the band forms usually reflects extension of the infection or pus formation."[56]

In reporting on the left shift and toxic granulation, the writer agrees with Wintrobe that no useful purpose is served by the construction of indices such as the Schilling Index for the former, and the Degenerative Index of Kugel and Rosenthal for the latter. "These devices are an attempt to give mathematical precision to a biological process which does not lend itself readily to mathematics. They tend to enshroud a relatively simple subject with an air of complexity and mysticism."[88] For all practical purposes it is sufficient to say that the left shift or the toxic changes are mild, moderate or marked as the case may be.

When Brucellosis is suspected it is important to differentiate between large and small lymphocytes and, in addition, it is necessary

- to -

to classify these cells into Wiseman's[92] Y, M and O forms. Calder, Steen and Baker[10] have shown that in Brucellosis there is (i) a preponderance of large over small lymphocytes even in adults, and (ii) an almost universal preponderance of Y forms. The Y forms are characterized by a deep blue (deeply basophilic) cytoplasm, no azur granules the nuclei often showing nucleoli. The M forms have moderately blue cytoplasm and no azur granules, while in the O forms the cytoplasm is very faintly blue with azur granules present. In 4/5 of the cases studied by Calder and his co-workers the Y forms exceeded very materially Wiseman's normal maximum of 5% which, expressed in absolute figures, means 100 of these young lymphocytes per cmm.

Wiseman's differentiation of the lymphocytes is also of importance when the question of Bed Fever has to be considered. It was pointed out on page 39 that prolonged bed rest after an infection, may, per se, be responsible for continued low grade fever. Reich and Reich[70] who made a study of the lymphocytes using Wiseman's[92] criteria have shown that the lymphocytes as well as the neutrophils take an active part in combating bacterial infection as shown by an increase in Y and M forms above the normal adult maximum of 5 and 45% respectively, and a decrease of O forms below the normal adult maximum of 50% "in practically all cases of infection." They declare that "a patient should not be regarded as entirely recovered from an infection until the lymphocytic formula has returned to normal." These considerations would, therefore, seem of practical importance in

deciding whether the prolongation of fever in any infection, when the temperature is expected to have dropped to normal, is due to a continuation of the infective process or to Bed Fever. These observers further claim that the Y lymphocytes are increased in mild as well as in severe infections and that this increase is a more sensitive indication of mild infection than is the relatively more stable filament non-filament count. To put it another way, the lymphocytic left shift is, according to these observers, a more sensitive index of mild infection than is the left shift of the neutrophils.

It is desired to express the view that in the diagnosis of obscure fever, as in any other clinical problem in which repeated haematological studies are required, the examination of the blood should be entrusted, both in private as well as in hospital practice, to a skilled haematologist. In the hospitals, at any rate in South Africa, it is the custom to leave the blood count to the inexperienced and overburdened resident physician. This should be discontinued. All haematological work should be placed on the same basis as any other laboratory procedure. That is to say, every hospital should have at its disposal the services of a trained haematologist. In voicing this opinion the writer is in complete accord with Wiseman's[91] declaration that "dependable blood examination requires the most exacting personal attention of a skilled haematologist." Wintrobe[88] likewise stresses the importance of being "critical about the blood count." Numerically expressed results, the latter authority points out, are apt to engender,

in the physician who reads them, "a sense of accuracy which may not be warranted unless the source of the information is above suspicion." A recent statistical analysis by Berg[3a] has shown that with perfect technique in the hands of an experienced haematologist an accuracy of ± 10% can be achieved in haemocytometry and haemoglobinometry, and that for clinical purposes an accuracy of this degree is more than sufficient.

In the investigation for the cause of an obscure fever, once the characteristic haemogram has been established by the method described, a given case will fall into one or other of the 7 haematological groups shown in Table 2. This at once connotes a very considerable narrowing of the vast field of differential diagnosis. Each group now becomes a unit, the components of which are susceptible to a differential diagnosis based on the clinical history and such nonspecific but helpful collateral clinical features as a disproportionate tachycardia, relative bradycardia, a cardiac murmur, continued intractable headache, joint pains without swelling, recurring chills, excessive or drenching sweats, symptomatic reference to the right or left upper quadrant or to the right lower quadrant of the abdomen or to a costovertebral angle, minimal constitutional disturbance, marked prostration, age incidence and residential history. In addition, as will have been gathered from the haematological survey, the blood picture is itself capable of contributing information of signal importance in the separation of the members of each haematological

group. The haematological classification has yet another and final attribute which is of special interest: every group contains within itself the indications for the appropriate special investigations to be undertaken for the purpose of establishing the diagnosis. The patient is thus saved from an haphazard battery of laboratory and radiographic tests.

The validity of these statements will be demonstrated in section (c) of this part of the thesis.

In the haematological classification submitted, a certain amount of overlapping is inevitable since some of the disease entities give rise to more than one leucocytic pattern. Thus, for example, Brucellosis may give rise to a mononuclear leucocytosis, leucopoenia or a normal total count with absolute lymphocytosis. Similarly, Subacute Bacterial Endocarditis while usually associated with a normal leucocyte count with neutrophilia, may atypically bring forth a neutrophil leucocytosis. An obscure fever which produces more than one white cell response will therefore be found listed in more than one group of the classification.

In conclusion it is desired to stress the importance of calculating from the total and differential leucocyte counts the absolute numbers of the various white cells per cmm. The presence of neutrophil leucocytosis, of mononucleosis, or of eosinophilia means an increase of these cells above their respective normal maximum, counted

in absolute figures per cmm.

The terms "mononuclear leucocytosis" and "mononucleosis" used in the table connote lymphocytes and monocytes and the respective figures represent the combined numbers of these cells.

Comment on the Value of the Erythrocyte Sedimentation Rate. Prolonged pyrexia due to an organic cause of whatever nature may be accompanied by a raised erythrocyte sedimentation rate. It follows, therefore, that in the etiological diagnosis of obscure fever a persistently normal sedimentation rate may be taken to mean that the cause is in all probability not organic. In the 51 possibilities listed in Table I pages 4 and 5 there are 4 such causes - da Costa's Syndrome, Neurogenic Fever, Spurious Fever and Bed Fever. Thus, when one or other of these conditions is suspected from the clinico-haematological evidence, a persistently normal E.S.R. would be confirmatory. It is necessary to point out, however, (i) that there is at least one organic cause of obscure fever in which the E.S.R. may remain normal for a variable period of time, namely, Chronic Fibrocaseous Pulmonary Tuberculosis, and (ii) that with more extensive serial studies of the sedimentation rate other members of the collection may be found to be associated, in their pre-clinical stages, with a normal sedimentation rate. Although it is not desired to stress the diagnostic significance of a normal E.S.R. it is probably right to say that for all practical purposes a persistently normal sedimentation rate, in the absence of radiographic

signs of pulmonary pathology, may be regarded as additional evidence in favour of the 4 possibilities mentioned. According to Farmer and Janeway[24] the E.S.R. is normal in the prodromal febrile stage of Lymphocytic Choriomeningitis.

There is only one other condition in which the sedimentation rate may be of value in diagnosis namely, Rheumatic Fever where the E.S.R. often remains raised after the subsidence of the pyrexia. In this regard Rheumatic Fever resembles only one other member of the obscure fevers namely, Chronic Phthisis.

(c) CASE STUDY ILLUSTRATING THE VALUE OF THE HÆMATOLOGICAL APPROACH IN THE ETIOLOGICAL DIAGNOSIS OF OBSCURE FEVER

D.J.P. a European clergyman 34 years of age was admitted to Groote Schuur Hospital, Cape Town, (Hospital Number 56991) on January 7, 1944, with pyrexia of undetermined origin of about 2 months duration. He left hospital still pyrexial on March 5, 1944.

The following routine bedside examination was conducted. Both the questionnaire and the physical examination were directed with particular reference to the elicitation of the causes of obscure fever shown in Table I. In the interrogation of the patient, especially in respect of the history of previous illnesses, the diseases thought of are placed in brackets after each question and the sequence of the interrogation follows the anatomical classification across Table I. The same scheme is used also in the physical examination.

Clinical History

Complaints

1. Anorexia and weight loss about 4 months
2. Irregular temperature with chills, sweats, generalized myalgic pains and malaise about 2 months

History of Onset

The patient was well until about 4 months ago. He then had an attack of "influenza." The symptoms were headache, watering eyes, a running nose and malaise. There were no body or joint pains. After 4 days of bed rest he felt better for about a week. He then developed a dull continuous pain in the left shoulder aggravated by movement. Medicine prescribed by his family physician failed to relieve the pain. About 2 weeks later he developed pain in the lower left chest aggravated by deep breathing and movement. His doctor reported an irregular temperature with chills and sweats, especially at night. He was confined to bed.

Family History

1. No family history of Rheumatic Fever
2. No family history of Tuberculosis
3. No family history of Carcinoma

Personal History - Nil of note

Residential History

1. No history of tropical residence. (Malaria, Visceral Leishmaniasis, Filariasis, Schistosomiasis)

Previous Illnesses and History of Contact

1. No history of Rheumatic Fever or of Chorea. (Polycyclic Rheumatism)
2. No history of recent dental extraction or tonsillectomy. (Subacute Bacterial Endocarditis)

3. No history of Otitis Media. (Lateral Sinus Thrombophlebitis, Brain Abscess)
4. No history of precordial pain, palpitation, fatigue or sighing. (da Costa's Syndrome)
5. No history of asthmatic attacks, chest pain, abdominal pain, polyarthralgia, muscle pains, Raynaud's phenomenon, numbness and tingling of the extremities, haematuria or multiform skin lesions. (Periarteritis Nodosa)
6. No cough (Pulmonary Tuberculosis) till about a month preceding his admission when a slight cough productive of a small amount of mucus developed. No staining. No haemoptysis. This episode lasted only a few days.
7. No history of contact with Primary Atypical Pneumonia.
8. No history of recent Lobar Pneumonia. (Encapsulated Empyema)
9. No history of depression, reticence, continuous intractable headache or of repeated vomiting. (Tuberculous Meningitis)
10. No history of spells of lightheadedness, euphoric emotional tone or of domestic mouse contact. (Lymphocytic Choriomeningitis)
11. No history of epistaxis, pea soup stools, constipation or continuous frontal headache during the first week. (Enteric Fevers)
12. No history either of peptic ulcer pain or of recurring appendicitis. (Subphrenic Abscess, Retrocaecal Appendix Abscess)
13. No history of muco-sanguineous diarrhoea. (Amoebic Liver Abscess)
14. No history of epigastric pain, haematemesis or melaena. (Carcinoma of the Stomach)

15. No history of right lower quadrant symptoms. (Regional Ileocolitis, Appendix Abscess)
16. No history of remissions of the fever or of recurring attacks of shooting right lower quadrant pain or of the passage of fatty stools. (Tabes Mesenterica)
17. No history of contact with Infectious Mononucleosis.
18. No history of Pel-Ebstein cycles with marked sweating and extreme prostration during the febrile episodes followed by intervening periods of apparent good health. (Hodgkin's Disease)
19. No history of recurring pyrexial bouts with transient oedema of the limbs. No history of tropical or sub-tropical residence with exposure to day and night biting mosquitoes. (Filariasis Nocturna)
20. No history of Furunculosis, Carbuncle, Quinsy or Alveolar Abscess. (Perinephric Abscess, Renal Carbuncle, Deep-seated Osteitis)
21. No history of renal colic or of hæmaturia. (Hypernephroma)
22. No history of exposure or drinking of snail infested water. No history of haematuria or of muco-sanguineous diarrhoea. No history of an urticarial eruption during the first week. (Schistosomiasis)
23. No history of the ingestion of swine flesh, diarrhœa, vomiting, muscle tenderness and pain aggravated by movement or of oedema of the bulbar and palpebral conjunctiva. (Trichiniasis)
24. No history of joint pains and swellings or of petechial haemorrhages. (Chronic Meningococcæmia)

25. No history of continuous headache, polyarthralgia or nervous manifestations. (Brucellosis) The night sweats and shoulder pain are, however, suggestive of Brucellosis.
26. No history of tick bites or of bites by the other insect vectors of the Rickettsial infections or of contact with patients suffering from these diseases.
27. No history of primary syphilis or of sore throat. (Secondary Syphilis)
28. No history of tropical residence. (Malaria, Visceral Leishmaniasis, Filariasis, Schistosomiasis)
29. No history of medication with sulphonamides, organic arsenicals, gold, dinitrophenol or thiouracil. (Drug Fever)

Physical Examination

A daily bedside examination was conducted with special reference to the elicitation of physical signs of the causes of obscure fever listed in Table I.

Cardiovascular System

1. No clinical enlargement of the heart. B.P. 155/95.
2. There was a soft non-conducted systolic murmur at the base. No diastolic murmur. No machinery murmur. (Subacute Bacterial Endocarditis complicating Patent Ductus)
3. No Osler's nodes, no subconjunctival ecchymosis. No machinery murmur over the peripheral vessels. (Subacute Bacterial Endocarditis complicating Arterio-venous Aneurysm)

4. No thickening, swelling or œdema over the jugular veins. (Pyogenic Lateral Sinus Thrombophlebitis)

Respiratory System

1. No apical crepitations, dullness or bronchial breathing. No physical signs whatever in the chest. (Chronic Phthisis, Primary Atypical Pneumonia, Miliary Tuberculosis, Empyema)
2. No paravertebral or parasternal dullness, D'Espine's sign negative. (Mediastinal Tuberculosis, Lymphosarcoma of the Mediastinal Glands, Mediastinal Hodgkin's)

Nervous System

1. No Kernig, no Brudzinsky, no neck rigidity. (Tuberculous Meningitis, Lymphocytic Choriomeningitis)
2. Fundi normal: no miliary tubercles. (Miliary tuberculosis, Tuberculous Meningitis). No papilloedema or congestion of the retinal veins. (Brain Abscess) No petechial haemorrhages in the retinæ. (Subacute Bacterial Endocarditis)
3. No bradyphrenia, no pyramidal signs, no cerebellar signs. (Brain Abscess)
4. No history of prolonged emotional tension. (Neurogenic Fever)
5. No symptoms or signs of peripheral neuritis. (Periarteritis Nodosa)

Digestive System

1. No mass in the right lower quadrant, no tenderness or spasm in the right lumbar region or para-umbilical region. (Retrocæcal Appendix Abscess)

2. No tenderness or enlargement of the liver and no right shoulder pain. (Amœbic Liver Abscess) About 3½ months after the beginning of the illness when an epigastric mass became palpable, a hard liver edge was distinctly felt at the right costal margin.
3. No epigastric mass (Carcinoma of the Stomach) until the 45th hospital day, that is about 3½ months after the beginning of the illness.
4. No palpable mass or tenderness in the right lower quadrant. (Regional Ileocolitis, Appendix Abscess)

Haemopoietic System

1. No abdominal masses could be felt. (Tabes Mesenterica)
2. No signs of mediastinal compression. (Lymphosarcoma of the Mediastinal Glands, Mediastinal Hodgkin's)
3. No peripheral lymphadenopathy. (Lymphosarcoma of the Mediastinal Glands, Infectious Mononucleosis, Acute Leukæmia, Hodgkin's Disease)

Urinary System

1. No tenderness, bulging or œdema at either costovertebral angle and no lumbar scoliosis. (Perinephric Abscess, Renal Carbuncle)
2. No hæmaturia or erythrocyturia. (Hypernephroma, Schistosomiasis, Periarteritis Nodosa)

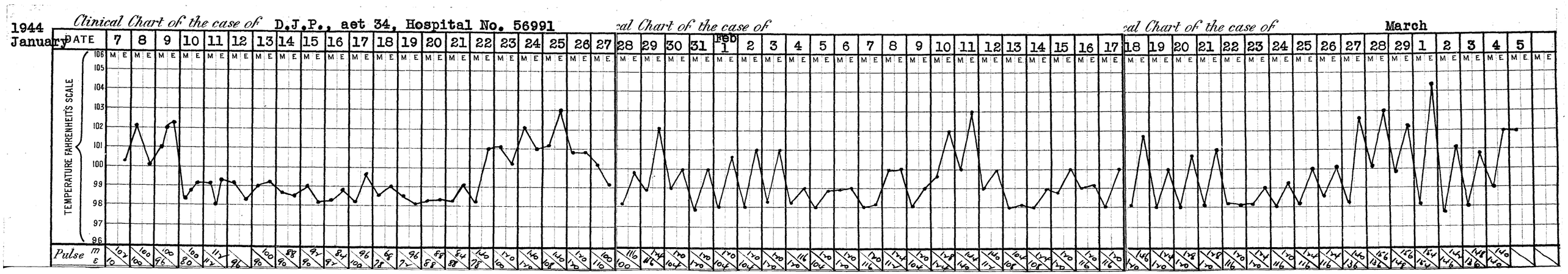
Locomotor System

1. No excessive tenderness of the skeletal muscles. (Trichiniasis)

Ear - No otorrhoea. (Lateral Sinus Thrombophlebitis, Brain Abscess)

Eye - No chemosis (Trichiniasis) or conjunctival petechiæ. (Subacute Bacterial Endocarditis)

The Temperature Chart



- Routine -

Routine Laboratory Tests

1. Routine blood culture repeatedly negative for
    (a) Streptococcus Viridans
    (b) Meningococcus
    (c) Streptococcus pyogenes
    (d) Staphylococcus pyogenes

2. Agglutination tests negative for
    (a) Enterica group
    (b) Brucella group
    (c) Proteus group

3. W.R. and Kahn negative

4. Urine culture repeatedly negative and no Bilharzia ova

5. Stools
    (a) Culture for Enterica group repeatedly negative
    (b) Examination for Entamoeba Histolytica and Bilharzia ova negative

The Serial Haemogram

Serial haemography was started on the second hospital day 8/1/44 and repeated on alternate days till January 18, 1944. Six haemograms were thus available for study as follows:-

The Serial Haemogram

	8/1/44	10/1/44	12/1/44	14/1/44	16/1/44	18/1/44
Total leucocytes per cmm.	8,550	7,400	7,200	8,250	9,230	10,600
Percentage neutrophils	65.5%	62%	65%	67%	70.5%	66.5%
Neutrophils per cmm.	5,600	4,588	4,680	5,528	6,508	7,050
Percentage filamented neutrophils	60%	40%	46%	48.5%	40.5%	54%
Percentage non-filamented neutrophils	5.5%	22%	19%	18.5%	30%	12.5%
Non-filamented neutrophils per cmm.	470	1,628	1,368	1,526	2,769	1,325
Toxic neutrophils	+	+ +	+ +	+	+ +	+
Lymphocytes	29%	30%	30%	28.5%	24.5%	26.5%
Monocytes	3.5%	5%	3.5%	4.5%	4%	5%
Eosinophils	1.5%	2%	1.5%	nil	1%	2%
Basophils	0.5%	1%	nil	nil	nil	nil
Erythrocytes per cmm.	3.1m.	3.4m.	3.2m.	3.0m.	3.1m.	3.4m.
Haemoglobin	54%	52%	51%	53%	52%	56%
Colour Index	0.88	0.76	0.80	0.88	0.84	0.82
General Survey of the Stained Film	nil of note	nil of note	nil of note	nil of note	nil of note	nil of note

Differential Diagnosis

The serial haemogram up to and including January 18, therefore showed (i) a total leucocyte count within normal range, (ii) a tendency to mild to moderate left shift of the neutrophils, (iii) mild to moderate toxic granulation, (iv) eosinophils present in normal numbers, and (v) a mild non-progressive low colour index anaemia. This obscure fever therefore fits into Group 4 of the haematological classification, (Table 2 pages 83 and 84) i.e. normal total leucocyte count with abnormal differential, the abnormality in the differential formula lying in the direction of mild to moderate neutrophil left shift with toxic changes in the neutrophils.

The haematological group into which this case falls contains 12 possibilities (vide Table 2 Group 4 p 84) which will be considered seriatim as follows:-

1. Subacute Bacterial Endocarditis suggested also by the recurring chills and a history of "influenza."

(a) The murmur. A soft non-conducted systolic murmur at the base is a common finding in pyrexia with anaemia from any cause. Furthermore, (i) no changes in the intensity or character of the murmur could be detected in the course of the daily routine bedside examination, and (ii) no murmur could at any time be heard at the apex or along the left border of the sternum. It was concluded, therefore, (i) that the murmur

was probably not organic and (ii) that the existence of infective endocarditis was, therefore, unlikely.

(b) The Serial Hæmogram. (i) The neutrophils in Subacute Bacterial Endocarditis rise and fall with the rise and fall of the total count but this fluctuation does not proceed pari passu with the fluctuations in the total count. In the serial hæmogram of the present case the neutrophil fluctuations tend to be more or less parallel with those of the total leucocyte count. (ii) Toxic granulation usually occurs in Subacute Bacterial Endocarditis only in the presence of embolic phenomena.[44] Here it was constantly present. (iii) An increase of the monocytes either relative (i.e. above 10%) or absolute (i.e. over 700 per cmm.) is usually found at one time or another in the serial hæmogram of Subacute Bacterial Endocarditis.[67] The monocytes were normal.

(c) There were no clinically demonstrable embolic phenomena (no Osler's nodes, no subconjunctival ecchymosis, no erythrocyturia).

(d) The routine blood culture was persistently negative.

2. Chronic Phthisis suggested also by chest pain aggravated by deep breathing. The routine chest radiographs taken on 8/1/44, i.e. the day following admission and 2 months after the commencement of the pyrexia, were both normal.

3. Brucellosis suggested also by the sweats and shoulder pain.

(a) Agglutination tests for the Brucella group, though negative, would not exclude Brucellosis (v. p 14).

(b) The Serial Hæmogram. When the total white cell count is persistently normal as it was in 50% of Calder's[10] cases there is invariably a relative or absolute increase of the lymphocytes. The anæmia is, furthermore, according to Calder et al.[10] largely macrocytic with the colour index above 1.15.

4. Acute Miliary Tuberculosis.

(a) Age incidence. Although it is generally agreed that the peak incidence of Acute Miliary Tuberculosis is in infants and young children no age is immune. (Chapman and Whorton[13]).

(b) The Course. In Chapman and Whorton's cases the longest course was 32 weeks. D.J.P. was discharged still pyrexial 6 months after the commencement of his illness so that Acute Miliary Tuberculosis cannot be ruled out on these grounds.

(c) Chest Radiograph. X-ray evidence of involvement of the lungs by the miliary process ("snow storm appearance") is rarely delayed beyond the 2nd week from the onset of symptoms and most modern writers state that the lungs are always involved. (Chapman and Whorton[13]). The chest radiograph was normal 4 months after the start of the illness.

- (d) -

(d) The Serial Hæmogram. The characteristic white cell response in Acute Miliary Tuberculosis is frank leucopoenia with neutrophilia, neutrophil left shift and toxic granulation. In 33% of Chapman and Whorton's[13] cases the total was within normal range, but the neutrophil percentages were, as a rule, distinctly raised despite a normal total white cell count. Percentages of over 80 were the rule with 96% as the top figure and the non-filamented forms frequently outnumbered the mature forms.[13] The left shift here was mild to moderate.

5. Primary Atypical Pneumonia also suggested by pleuritic pain.

(a) Relative bradycardia is usual. This case showed if anything a tendency to disproportionate tachycardia.

(b) Positive radiographic findings in the chest appear in from 1-4 days from the onset.

(c) There is no anæmia.

6. The Rickettsial Diseases.

(a) The Serial Hæmogram. In African Tick-Bite Fever and in Epidemic Typhus relative monocytosis is a striking feature (Kugelmass[45]) and the eosinophils tend to disappear.

(b) The Weil-Felix was negative.

7. Carcinoma of the Stomach. The Serial Haemogram is in keeping with this diagnosis.

8. Infectious Lymphocytosis. Although there is a recorded case of Infectious Lymphocytosis in which the pyrexia continued for 4 years, the blood picture in adults is characterized by a mononuclear leucocytosis. Furthermore, there is no anæmia.

9. Acute Aleukaemic Leukaemia.

(a) Age incidence. The peak incidence is in the first 5 years of life; it is rare after 25. Marked prostration is early and there is a rapidly progressive anæmia with outspoken thrombocytopoenia. Prostration was absent and platelets were plentiful.

10. Hodgkin's Disease (Primary in the deep nodes of the mediastinum or abdomen or primary gastro-duodenal Hodgkin's).

(a) According to Jackson and Parker[39a] the appearance of peripheral lymphadenopathy is hardly ever delayed beyond 6 months. The patient left hospital 6 months after the commencement of his illness without enlargement of any of the groups of accessible lymph nodes.

(b) The Haemogram is in keeping with Hodgkin's disease in all respects save the presence of toxic granulation of the neutrophils. Toxic cytoplasmic changes have not been recorded in Hodgkin's Disease. (Kugel and Rosenthal[44]).

11. Deep-seated Suppuration.

(a) The Blood Picture. While neutrophil leucocytosis is the rule in deep-seated suppuration, the total neutrophil counts may remain normal. Although eosinophils are classically either absent altogether or reduced (Schilling[75]) the presence of eosinophils in normal numbers does not exclude the possibility.

(b) The Clinical History. Deep-seated suppuration may be excluded on clinical grounds with particular reference to the history of previous illnesses. Deep-seated abscess is unlikely in the absence of a history of antecedent conditions of which deep-seated suppuration in the anatomical situations defined in Table I is a complication. Let us consider the group of deep-seated abscesses in the order in which they appear in Table I.

(i) Pyogenic Lateral Sinus Thrombophlebitis and Brain Abscess. Purulent otitis media is the commonest antecedent in both these conditions. There was no such history.

(ii) Encapsulated Empyema. Empyema in general and the encapsulated variety in particular may follow in the wake of a recent lobar pneumonia of which there is no history.

(iii) Subphrenic Abscess, Retrocæcal Appendix Abscess. There is no history of recurring appendicitis or of peptic ulcer pain to suggest a complicating subphrenic abscess or of a retrocæcal appendix abscess.

(iv) Amœbic Liver Abscess. The absence of a history of muco-sanguineous diarrhœa does not, as is well known, exclude the possibility of amœbic liver abscess. In Sodeman and Lewis'[78] series only 32% of proved cases of amœbic liver abscess gave a history of the passage of blood and mucus per rectum. On the other hand, while clinical hepatomegaly may be notably absent, Sodeman and Lewis[78] declare that tenderness in the region of the liver occurs in 100% of cases. There is almost always vague discomfort or a dull ache in the right upper quadrant. Neither could be elicited in the present case.

(v) Perinephric Abscess, Renal Carbuncle and Deep-seated Osteitis are commonly preceded by furunculosis, carbuncle, quinsy or alveolar abscess. These surface infections are often accompanied by a clinically silent and uneventful bacteraemia which may be followed by a metastatic fixation abscess either in the perirenal fat with the production of a perinephric abscess in the renal cortex resulting in a renal carbuncle, or in bone

with a resulting osteitis. The subjects of deep-seated osteitis, usually in the pelvic girdle, are largely children.

12. Periarteritis Nodosa.

(a) The Serial Haemogram. Normal total leucocyte counts are very infrequent in Periarteritis Nodosa. Furthermore, when the white cell count is within normal limits the eosinophils are usually outspokenly raised. (Lubowich and Hunt[50]).

(b) The onset with influenzal symptoms would go for Periarteritis Nodosa. But, while fever may remain the only sign for some weeks, symptomatic reference to an organ or tissue, more especially the kidney with glomerulonephritis, the bronchioles with asthmatic attacks, or the peripheral nerves with the symptomatology of peripheral neuritis (Grant[29]) would be expected after 2 months of pyrexia and 4 months after the beginning of the illness.

On this clinico-haematological evidence together with the routine chest radiograph and the special laboratory tests which were made, all the members of Group 4 of the haematological classification can be reasonably excluded except Carcinoma of the Stomach. That gastric cancer can present with prolonged clinically silent fever has already been indicated (v.p 25). It was decided, therefore, to advise an opaque meal and the following is the radiologist's report dated 25/1/44:

"1. As a result of the barium meal examination it was found that there was a persistent irregularity of contour and contraction of the pyloric end of the stomach. The rugae in this region are fainter than in the more normal proximal part of the stomach and are not interrupted but rather fainter as though pressed upon. In some of the views there is a rounded filling defect of the barium pattern here. Peristalsis stopped short of the site of the abnormality. There was no fixity of the stomach nor could a tumour be palpated here.

2. The appearances were quite unaltered by intensive antispasmodics.

3. Visible metastatic deposits resulting in contoural abnormality are seen in the 11th rib at its inner end and in the 3rd lumbar vertebra.

Conclusion:- It is difficult to decide definitely whether the stomach is the seat of a carcinoma or of an infiltrative process from a reticulosis viz Hodgkin's disease. The main points in favour of the latter are the appearances of the rugal pattern and the flexibility. The peristalsis however, is more in favour of a carcinoma. The metastases are not distinctive and could occur in either."

A fractional test meal was done on 7/2/44 with the following results showing histamine refractory achlorhydria.

	Free Hcl.	Total Acid	Blood	Mucus
Fasting fluid 40cc	nil	30	+	+
1st specimen	nil	insufficient	nil	+
2nd specimen	nil	11	nil	+
3rd specimen	nil	9	0	+
4th specimen	nil	7	0	+
5th specimen	nil	9	0	0
Histamine				
6th specimen	nil	10	0	+
7th specimen	nil	7	trace	+
8th specimen	nil	insufficient		
Residual fluid 1cc	nil	insufficient	nil	0

The serum alkaline phosphatose on 28/1/44 was 36 Bodansky units (normal 1.5 to 4 Bodansky units).

On 2/2/44 the blood count was as follows:- Total leucocytes 6,900, percentage neutrophils 62, (filamented 42%, non-filamented 20%) toxic granulation + + , lymphocytes 31%, monocytes 4%, eosinophils 2%, basophils 1%, erythrocytes 1.82 million, haemoglobin 30%, colour index 0.83. Myelocytes constituted 9% of the non-filamented forms. Six normoblasts were identified in the course of a count of 400 white cells. Platelets were plentifully represented.

On 6/2/44 a colleague thought he could feel a lump in the upper abdomen but the unequivocal presence of a lump could only be demonstrated on the 45th hospital day, i.e. about 3½ months after the inception of this silent pyrexia. At the same time a hard liver edge was distinctly felt at the right costal margin.

The radiologist's report left us with 2 possibilities, namely, Primary Gastric Hodgkin's Disease with marrow involvement, and Gastric Carcinoma with bone secondaries, with the radiologist's bet in favour of the latter. It is here that the blood picture again makes its contribution to the differential diagnosis. The first blood count on admission showed a distinct anaemia while the last count on 2/2/44 revealed what amounts to a leuco-erythroblastic blood picture: Anaemia, nucleated reds, immature white cells with platelets plentifully represented. Jackson and Parker[39b] in their study of bone marrow Hodgkin's declare that in the presence of most extensive bone changes "neither the red cell nor the white cell count altered in any material manner ... even at the time of death ... contrariwise, leuco-erythroblastic anaemia is to be expected in carcinomatous metastasis to the marrow." Our blood findings were, therefore, distinctly against marrow Hodgkin's and in favour of carcinoma. Two additional facts militate against the diagnosis of Primary Gastric Hodgkin's Disease:-
(i) Hitherto no case of primary gastro-intestinal Hodgkin's presenting with cryptic fever has been recorded in any situation other than the

duodenum. (Jackson and Parker[39a]). (ii) Involvement of the peripheral glands almost always makes its appearance within 6 months from the beginning of the illness.[39a] The patient left hospital after a six months illness without peripheral lymphadenopathy.

This study of a case of "Pyrexia of Undetermined Origin" therefore illustrates the following points:-

1. Prior to the evidence made available by the serial haemogram this pyrexia of at least 2 months duration without localizing signs or symptoms embraced a large number of the possibilities listed in Table I.

2. Repeated routine blood counts (six haemograms, one on alternate days) revealed the design of the leucocytic pattern which fitted Group 4 of the haematological classification in Table 2. The field of possibilities was thus narrowed down to 12.

3. From a differential diagnosis of the 12 members of this group in which the blood picture played an important role, the further study of this case, with particular reference to the appropriate special investigations to be undertaken, became apparent.

4. The provisional diagnosis which emerged from the clinico-haematological study was supported by radiography. The radiologist's suggestion of a second alternative was further excluded on a

clinico-haematological basis with the blood picture once more contributing valuable diagnostic information.

This case study also illustrates the main theme of this thesis, namely, the value of the haematological approach in the etiological diagnosis of "Pyrexia of Undetermined Origin." It further serves to demonstrate how the list of the possibilities submitted in Table I pages 4 and 5 is utilized in planning the clinical investigation.

I am indebted to Dr. P.J. Keet, Hon. Physician at the Groote Schuur Hospital, for his kind permission to study this case.

SUMMARY AND CONCLUSIONS

1. The first requirement for the diagnosis of the cause of an obscure fever is a high degree of alertness to the possibilities to be considered. Failure to diagnose the cause is more often due to failure to think of it than to any other single factor.

2. A classified list is submitted as a comprehensive practical guide to the possibilities to be considered in the differential diagnosis of a given case of fever which either continues past the 10th day or recurs in cycles of variable duration without the emergence of localizing symptomatology.

3. Evidence is adduced to show that each of the disease entities listed is a potential cause of obscure fever.

4. The second requirement in the elucidation of the cause of an obscure fever is to find a starting point for breaking up this large field of possibilities into a series of smaller groups for differential diagnosis.

5. From a detailed study of the peripheral blood responses of the 51 affections presenting with obscure fever the thesis is propounded that the serial haemogram constitutes an eminently satisfactory basis for such a diagnostic classification.

6. A haematological classification has been worked out founded on serial haemography.

7. A case study is appended to illustrate the main theme of this thesis, namely, the value of the haematological approach in the etiological diagnosis of "Pyrexia of Undetermined Origin."

SUGGESTIONS FOR FURTHER STUDY

1. It is recommended that the serially repeated routine blood count form an integral part of the etiological investigation of obscure fever. No detailed blood studies are at present available for the following diseases which are potentially responsible for obscure fever: Tuberculosis of the Mediastinal Lymph Glands, Tuberculous Meningitis, Tabes Mesenterica, Chronic Miliary Tuberculosis, Hypernephroma, Chronic Nasopharyngitis and Pink Disease. It is only by routine serial hæmography that these gaps can be filled in. Furthermore, with the routine practice of serial hæmography further evidence will be made available to check up on the peripheral blood responses which have been described.

2. The routine blood count should include (i) the differentiation between filament and non-filament neutrophils according to the criteria of Cooke and Ponder and (ii) the examination for toxic cytoplasmic changes in these cells. It would seem also that more attention should be directed to the differentiation of the lymphocytes according to Wiseman's criteria.

3. The haematological studies should be delegated to a trained and experienced haematologist.

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