A CRITICAL STUDY OF UNDULANT FEVER.

FROM A SERIES OF SIX CASES IN THE HOSPITAL FOR TROPICAL DISEASES, LONDON.

BY

PHILIP MANSON-BAHR, D.S.O., M.D., F.R.C.P.,
PHYSICIAN TO THE HOSPITAL FOR TROPICAL DISEASES, ENDSEIGH
GARDENS, LONDON;

AND

HUGH WILLOUGHBY, M.R.C.S., L.R.C.P.,
D.T.M. and H.

LATE HOUSE-PHYSICIAN TO THE HOSPITAL FOR TROPICAL DISEASES.

UNDULANT fever (formerly known as Malta fever) is becoming sufficiently rare in practice in England to excite comment whenever it occurs, while the close association, or identity, of *abortus* fever in man and cattle with the classical type of undulant fever is at present attracting universal attention. We therefore consider it an opportune moment to survey a series of cases which have occurred in the practice of this hospital during the last eight years. It shows clearly enough, from the localities from which the patients were derived, the almost universal distribution of undulant fever, for here we have for comparison a series of cases derived from India, East Africa, Peru, and from England itself. No cases, however, have come from the Mediterranean.

There are several points upon which we are at liberty to comment, as can be gathered from the accompanying tables.

DIAGNOSIS.

First, as regards the initial diagnosis, it is noteworthy that the impressions recorded were those of typhoid in four cases, malaria in another, and influenza in the sixth. Added to this we might mention that the localization of pain to the margin of the gums and to the eyes in the initial stages of the fever first drew attention to possible defects in these organs. It is fair to state that in making these initial tentative diagnoses there was some justification of a diagnosis of typhoid or malaria in the previous history of the patient. Nevertheless, we can say that all the cases, surveyed as a whole, presented a definite diagnostic syndrome. In this category we include a high initial remittent pyrexia, and it is necessary to emphasize that this may be high (up to 105° F.), resembling in this respect that of true typhoid (see charts). Splenomegaly of a considerable degree was present in every case, and should be considered a prominent factor in making a diagnosis. The intradermal "melitene" reaction of Burnet was tried in three instances and proved to be successful. The skin reaction remained visible for forty-eight hours.

SYMPTOMS.

Arthritic pain was a constant and characteristic feature associated with periarticular effusions which are particularly transient, appearing first in one joint, and then, after a short interval, in a neighbouring one. In addition to the joint pains, the fasciae and bony prominences exposed to the greatest amount of pressure are also affected. We would emphasize that the headache of undulant fever, which is so persistent in the early stages of the infection, has a characteristic of its own. It is not so dull or stuporose as that of typhoid, but it causes intractable insomnia without any appearance of delirium or dulling of the mental faculties. Another characteristic which would assist the practitioner in the differential diagnosis from typhoid is the epistaxis which appears early in the typhoid group, but correspondingly late in the course of undulant fever. It is really part of a general tendency to haemorrhage, as instanced by the bleeding from the gums in three cases, for which the patients had all their teeth removed in the initial stages of the illness. Purpuric eruption resembling that of scurvy appeared in one, and in one particularly protracted case frequent haemorrhages from the urethra were recorded.

Rigors of a sub-acute character were frequently noted in three cases, with the exacerbation of the fever following upon a comparatively quiescent period. These signs may be taken as affording additional evidence in the differential diagnosis from typhoid, in which they are rare.

The tendency in the later stages of the disease for *Brucella melitensis* to spread by the lymphatic route (a method of spread which is found also in *Br. abortus* in cattle) is one to which hardly sufficient attention has been drawn. There occurs a specific adenitis in this disease (about the fourth month).

The glands affected were the cervical group in three, the inguinal set in three, and in two the symptoms were referred to the intra-abdominal glands at the portal fissure, which, if unrecognized, might lead to the suspicion that the patient was suffering from some affection of the gall-bladder. That orchitis may supervene in undulant fever has long been recognized, and it is probably of the same nature as the adenitis already referred to. Testicular pain with some degree of enlargement of the organs themselves was observed in half the number of cases. Profuse and drenching sweats were noted in all. The sweating is universal and occurs mostly at night, necessitating the frequent changing of the bedclothes. A peculiar sour and penetrating odour characterized the sweats in two instances—the "tang" of the odour somewhat resembling that of typhoid to those who are able to appreciate it.

It is hardly necessary for us to comment upon the characters of the temperature charts which are reproduced herewith and which show the curious rhythmical variations. From the figures worked out from our charts the tendency

CASE 1.

CASE 2.

CASE 3.

Charts in the first ten weeks of the fever in three cases, showing variations in type of temperature.

TABLE I.—Clinical Symptoms.

Symptoms.	Case 1.	Case 2.	Case 3.	Case 4.	Case 5.	Case 6.
Fever	+	+	+	+	+	+
Sweats	+	+	+	+	+	++
Arthritis	+	+	+	+	+	+
Spleen	+	+	+	+	+	+
Headache	+	++	+	+	++	+
Adenitis	+	+	—	—	+	—
Eye pains	+	+	+	+	+	+
Photophobia	+	+	—	+	—	—
Sore throat	+	—	—	—	+	—
Haemorrhage:						
1. Epistaxis	+	+	+	+	+	+
2. Gums	—	+	+	+	—	—
3. Urethral	—	+	—	—	—	—
4. Purpura	—	—	+	—	—	—
Testicular pain	—	—	+	+	—	+
Sudaminary odour	+	—	+	—	—	—

is for the maximum* rise of temperature to take place between 6 and 10 p.m. The lowest temperatures on an average are recorded between 10 a.m. and 2 p.m.

SEQUELS.

Amongst the distressing sequels noted were sciatica of a most persistent character lasting for weeks, and once with pain localized to the sacro-iliac joints, possibly brought about by haemorrhage into the joint cavity. Muscular wasting and laxity of the ligaments of the knee and foot causes a considerable degree of disability during convalescence.

CLINICAL PATHOLOGY.

An analysis of the clinical pathology shows that the blood count throughout all the stages of undulant fever is generally normal. No rise in the number of leucocytes was noted in any instance. On the other hand, one case showed definite changes in the red blood corpuscles, and this was

TABLE II.—Pathological.

	Case 1.	Case 2.	Case 3.	Case 4.	Case 5.	Case 6.
R.B.C.	4,900,000	4,770,000	3,420,000	5,030,000	—	4,000,000
W.B.C.	8,110	7,200	4,400	6,900	6,900	8,600
Hb.	85%	85%	75%	90%	—	80%
Polymorphs	48%	—	50%	37%	—	42%
Lymphocytes	44%	—	42%	50%	—	46%
Mononuclears	7%	—	8%	16%	—	12%
Eosinophils	1%	—	0%	3%	—	0%
Parasites	Nil	Nil	Nil	Nil	Nil	Nil
Anisocytosis	—	—	Anisocytosis	—	—	—
Poikilocytosis	—	—	Poikilocytosis	—	—	—
Blood culture	Positive once only	Positive once only	Positive on two occasions	Negative throughout	Positive once only	Negative throughout
Urine culture	Negative throughout	Negative throughout	Positive once only	Negative throughout	Negative throughout	Negative throughout
Agglutinates:						
<i>Br. melitensis</i>	1 in 640	1 in 80	1 in 1,280	1 in 640	1 in 630	1 in 500
<i>B. typhosus</i>	—	—	—	1 in 320	—	—
<i>Br. abortus</i>	—	—	—	1 in 480	—	—

due undoubtedly to persistent purpura (Case 3). *Br. melitensis* was isolated by blood culture in four instances, and

* Maximum rises: 2 a.m., 7 per cent.; 6 a.m., 14 per cent.; 10 a.m., 2 per cent.; 2 p.m., 6 per cent.; 6 p.m., 33 per cent.; 10 p.m., 38 per cent.

it is to be noted that the organism can be isolated from the blood stream at any period of the disease up to absolute convalescence, even when the patient's condition would not lead one to suspect a septicaemia, and it is probably true that the organism is not actually destroyed in the blood stream, but that the infection "burns itself out." It is to be noted, too, that in order to secure success in blood culture the inoculated medium must be incubated for at least ten days; the same applies to the cultivation from the urine. In one instance success was obtained from a mid-stream specimen which proved to be uncontaminated; on the other hand, no success was obtained with catheter specimens.

SEROLOGICAL TESTS.

The agglutination test with dead emulsions of *Br. melitensis* (Mediterranean strain) proved of diagnostic value in every case when performed by the macroscopic method. On each occasion the initial diagnosis was made by this test on Garrow's agglutinator, which proved to be as reliable, and much more expeditious, than the tube method. We would emphasize that the titre of agglutination appears to have no bearing on the prognosis, nor does it indicate in any way the probability of isolation of the organism by blood culture. For instance, in the most severe case of our series (Case 2) the titre of agglutination to *Br. melitensis* never rose above 1 in 80.

TREATMENT.

On the question of treatment it is a matter of regret that we have nothing very positive to record. As regards the efficacy of vaccine we prefer to keep an open mind. As will

TABLE III.—Treatment.

	Vaccines—				Other Treatment.
	Stock.	Autogenous.	Med. Res. Council.*	Bacillus typhosus.	
Case 1	Million. 98	Million. 310	Million. 1,300	—	Rectal argochrome 1.8 gm.; N. A. B. 0.3 gm.
Case 2	—	1,275	—	—	—
Case 3	100	900	—	—	N. A. B. 0.95 gm.
Case 4	—	—	—	400	—
Case 5	—	125	—	—	—
Case 6	475	—	—	—	—

* Polyvalent (Douglas).

be seen by Table III, all varieties of vaccines were tried. The effect of stock vaccines made from standardized laboratory cultures of *Br. melitensis* in doses of from 60 to 300 million were compared with those of autogenous vaccines made from organisms isolated from blood culture and with a polyvalent vaccine issued by the Medical Research Council and composed of many strains. We could obtain no evidence that the use of vaccines given over a prolonged period of three months or more in any way modified the course of the disease.

TABLE IV.—Miscellaneous.

	Duration of Illness.	Infecting Agent.	Place of Infection.	Profession of Patient.
Case 1	12 mths.	Traceable to goats carried on board	Indian waters	Ship's engineer
Case 2	15 mths. +	Laboratory cultures of Case 3	London	Pathologist
Case 3	9 mths.	Goat's milk and cream cheese	Lima, Peru	Engineer (civil)
Case 4	5 mths.	? Cow's milk	Kent	Colonel (ret.) farmer
Case 5	4 mths.	Goat's milk	Djibouti, Somaliland	Wife of a planter
Case 6	5 mths.	Goat's milk	Djibouti	Planter

Argochrome, a silver methylene blue compound prepared by Merck's and recommended by Nocht, was tried in one case by rectal enema. Although the methylene blue was absorbed and appeared in the urine, it seemed to have no

beneficial effect at all. Intravenous injections of eusol in doses of 50 c.cm. (double strength in distilled water) was tried in one case, and appeared to have some influence in modifying the fever.

In conclusion we would like to acknowledge our indebtedness to Dr. J. T. Duncan of the London School of Hygiene and Tropical Medicine, and Messrs. F. W. Foster and W. J. Muggleton for their kind assistance with the laboratory work undertaken in connexion with the above series of cases.

AN IMPROVED DIFFRACTION METHOD FOR DIAGNOSING AND FOLLOWING THE COURSE OF PERNICIOUS AND OTHER ANAEMIAS.*

BY

ADRIANUS PIJPER, M.D.,

PATHOLOGIST TO THE PRETORIA HOSPITAL, PRETORIA, SOUTH AFRICA.

Principle of Method.

WHEN a beam of white light is sent through a blood smear it is broken up (diffracted) by the blood cells into the spectral colours. From the distribution of the colours the mean diameter, the degree and quality of anisocytosis, and the degree of poikilocytosis of the red cells can be determined. The application of the method is simpler than the description. No mathematics are required to read Figs. 3 to 11, where the half-circles illustrate the diffraction spectra exactly as they appear on the screen of the apparatus, two at a time, thus facilitating comparison and reading of results. "Diffraction method" and "diffraction micrometer" are suggested as suitable names.†

Need for Method.

The increasing incidence in many countries of Addison's (pernicious) anaemia,⁴ together with Minot and Murphy's discovery of the liver treatment,⁵ has led to the publication of numerous papers. A curious feature of this literature is the scantiness or absence of numerical data on the diameter of the red blood cells, although the correctness of Hurst's statement,⁶ "the most characteristic features of the blood in Addison's anaemia are the anisocytosis and the increase in the average size of the red cells," is at the same time very generally admitted. Red cell measurements evidently are still universally regarded as "research," and not as "routine." This is due to the lack of a suitable method. Direct microscopic measurement,⁷ and photographic methods,⁸ are manifestly too laborious.

Advantages of Method.

In its present form the advantages of the method are:

1. The only material required is a properly made, unfixed, unstained blood smear. Such smears remain serviceable for years, thus allowing dispatch over long distances, and storage for future reference. Fixed and stained smears are less suitable.
2. The method expresses in tenths of microns the mean diameter of at least one million red cells.
3. The method expresses in tenths of microns the diameter of both the largest and the smallest cells which are present in the smear in considerable number. In other words, it gives the degree and quality of the anisocytosis present. The information thus gained is not sufficient to construct a frequency curve, but ample for practical purposes, as it indicates the essential features of the curve.
4. The method gives the degree of poikilocytosis present in the blood smear.
5. All these determinations together do not take more time than a haemoglobin estimation.

* Part of the apparatus used in working out the diffraction method was bought by aid of a grant from the Union Government Research Grant Board.

† It has repeatedly been brought to my notice that Thomas Young (1773-1829) employed the identical principle, first for the measurement of wool fibres (wool=erion), and later of red blood cells. I cannot regard this as a reason to call my apparatus an erionmeter, as Emmons¹ has suggested. When, in 1918, I discovered that bacterial colonies can produce diffraction spectra, I started using this phenomenon for measuring bacteria.² From this beginning I developed my diffraction method of measuring red cells³ in complete ignorance of Thomas Young's work.

6. The cost of the apparatus is moderate.

7. The method allows the direct comparison of the essential characteristics, mentioned above, of any two blood smears. This is helpful in following the course of a disease. (See Figs. 9 to 11.)

As I am dealing with practical issues only, I shall not go into the controversy about the effect of drying upon the diameter of the cells, nor discuss the problem whether there is such a thing as "the exact diameter" of a red cell.

Theory of Method.

The thin end of a properly made blood smear can be regarded as a diffraction-grating, the cells being opaque and the plasma transparent. A beam of white light passing at right angles through such a smear is diffracted at the edges of the cells, and the resulting light waves, collected by a lens placed behind the blood smear, will produce a series of concentric circular spectra in the focal plane of the lens. The size of these spectra is a function of the diameter of the red cells of the smear, the white cells being too few to count.

For practical purposes only the innermost of the circular spectra need be considered, as being the brightest. The formula expressing the relationship between the various factors, the derivation of which can be found in textbooks on physics, is:

$$d = \frac{1.7\lambda \sqrt{f^2 + r^2}}{r}$$

in which (d) is the diameter of the red cells, (f) the focal distance of the lens used, (r) the radius of the coloured circle in the (innermost) spectrum, and (λ) the corresponding wave-length. The formula shows that the diameter of the cells can be calculated from the radius of any coloured circle, that the diameter of the coloured circles and the diameter of the cells vary inversely, and that a lens with a longer focal distance will produce larger spectra.

So far the matter has been treated as if the elements of the diffraction-grating (the red cells) were all of equal diameter. The diameters of the red cells of a healthy person, of course, follow the curve of normal variation. Therefore, assuming that the mean diameter in such a case is 7.3μ , there will be more cells of this diameter than of any other, but there will also be an ever-decreasing number of cells deviating more and more, in opposite directions, from this mean value. The spectrum produced by the cells measuring 7.3μ will naturally be the brightest, these cells being the most numerous. On this spectrum will be superimposed the weaker spectra belonging to the other, smaller and larger, cells. In Fig. 1 are drawn to scale, as calculated from the formula, the spectra thrown by cells measuring 7.3 , 6.7 , and 7.9μ . Intermediate cells will, of course, throw intermediate spectra. The drawing shows that all these superimposed spectra will practically not affect the position of the bright yellow circle produced by cells measuring 7.3μ . They will make the whole yellow circle broader, and the superimposed red and green will dilute the colour. This means that the brightest yellow circle will remain the expression of the mean diameter of the red cells, and that from that yellow circle the mean diameter can be calculated (wave-length 0.59μ).

From Fig. 1 it is also obvious that the innermost violet circle always is the expression of the largest cells present in a blood smear in sufficient number to produce visible colours, and that similarly the outermost red circle represents the smallest cells which are present in the blood

FIG. 1.