THE EPIDEMIOLOGY AND CONTROL

OF PHLEBOTOMUS FEVER.

The Use Of D.D.T.
In The Control Of The Outbreak Among
Naval Personnel In Malta During 1945.

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INTRODUCTION.

There had been a large outbreak of phlebotomus, or sandfly fever, among naval personnel in Malta in 1944, and it seemed probable that a similar outbreak might be expected to occur in 1945. Such an event would have seriously interfered with the efficiency of the naval base. It would, moreover, have complicated the training and manning of the H.M. ships which were using Malta as a final 'working up' base, prior to joining the Fleets in the Far East for the war against Japan. It, therefore, became operationally important that the number of cases of sandfly fever occurring during the summer of 1945 should be kept as low as possible.

The military significance of this disease has been stressed by Megaw (1944) and others. Sabin and his co-workers (1944[1]) stated that while the disease was self limited and there were no fatalities, its military importance lay in the fact that it could incapacitate large numbers of men for periods of seven to fourteen days or longer at a time when their services might be needed most.

Owing to the habits of the vector, and the infection of the immature phlebotomus in the breeding grounds, control of the spread of this disease has always been difficult. The measures advised by Whittingham and Rook (1923[1]) in their classical paper entitled "The Prevention of Phlebotomus Fever" are more suited for peacetime establishments than active service conditions, and require time, materials and much labour. These were not available in Malta in the early months of 1945 as the naval base had an important role to play in the strategy of the war in Italy, and in the Pacific. At the outset, the epidemic showed signs of being at least as severe as in the previous year. However, supplies of the insecticide 1. 1 bis (p -chlorophenyl) - 2. 2. 2 trichloroethane, commonly called DDT, arrived in June. It is my submission that largely by the use of this substance the epidemic was controlled.

The scope of this Thesis is:-

(1) To review and summarise existing knowledge of phlebotomus fever, and record certain original observations.

(11) To describe the properties and action of DDT, together with the methods of use and personal experience with the insecticide.

(111) To discuss the epidemiology of the disease, with special reference to the outbreaks among naval personnel in Malta in 1944 and 1945.

(1V) To describe the measures used for the control of the 1945 epidemic, and discuss the results obtained.

These observations were carried out in Malta from February, 1945, till December, 1945, whilst I was serving as Naval Health Officer on the Staff of Vice-Admiral, Malta, and Central Mediterranean Area. I was responsible for advising on the preventive measures to be adopted, and for the administrative direction of the scheme for the control of the epidemic. I examined some 500 cases of sandfly fever, and made a detailed study of 153 cases.

I wish to express my indebtedness to Surgeon Captain W. H. Murray, R.N, the Medical Officer in Charge of the Royal Naval Hospital, Malta, for encouragement and advice. My thanks are due also to my predecessor, Surgeon Commander R. J. Matthews, R.N.V.R, whose records provided the basic data for the study of the outbreak in 1944. I am beholden to Sick Berth Petty Officer (Sanitary Inspector) D. Redgewell, and Leading Sick Berth Attendant, G. T. W. Davies for assistance with record keeping. These ratings also taught control methods to the anti-sandfly parties in H.M. Ships and Establishments. Not least are my thanks due to the Senior Medical Officers and others in Malta for interest shown in the investigation, and for assistance in the collection of accurate records.

Section 1.

Review Of Existing Knowledge, Together With Certain Original Observations.

Definition.

Phlebotomus fever is a specific fever of short duration which is characterised by severe frontal headache, flushed face, suffused conjunctivae, tender eyeballs and photophobia; pains in the back, limbs and eyes; slow pulse, anorexia and prostration. The infective agent is an ultramicroscopic virus which is introduced by the bite of a midge of the genus Phlebotomus. The fever lasts on the average three days. There is no mortality, but convalescence may be slow and accompanied by weakness and mental depression.

Names for the Fever.

The disease is nowadays known as phlebotomus fever, or sandfly fever. The former is the better name, as the vector is not ordinarily connected with sand, and the term 'sandfly' is applied loosely to different insects in various parts of the world. As Newstead (1911) pointed out, the papatasii flies belong to the genus Phlebotomus - that is, the blood sucking psychodid flies. It would appear that the usual biting insects found in sandy places belong to the genus Culicoides, (Sabin et al. 1944[1]). In my experience, the common 'sand-fly' which bites bathers in the Mediterranean area at dusk is a culicine mosquito. In Malta, this insect, which is a particularly vicious biter, breeds in salt water pools or salt pans on the rocky foreshore.

In the past, the fever has been described under a variety of names. The commonest were pappataci fever, three day fever, Mediterranean dengue, summer influenza, summer fever, febricula, simple continued fever, soldaten fieber, acclimatization fever, endemic climatic gastro-enteritis, Chitral fever, and hundskrankheit or 'dog disease'; the flushed facies with the bloodshot eyes was thought to resemble the face of a mastiff.

Historical.

The earliest reports of the disease indicate that it was recognised clinically at the beginning of the 19th Century (Birt 1910[1], Birt 1913, Whittingham 1922[1]). Pick (1886) has been credited as the first observer to have described the condition as a clinical entity. Birt (1910[1]) quoted a description of the disease written in 1804 by Pym, an Army Medical Officer, then gave the following extract from a treatise on the subject by a famous Naval Surgeon:-

> "William Burnett (A Practical Account Of The Mediterranean Fever, 1816) states:-
>
> "Towards the end of June or commencement of July slight attacks of fever begin to present themselves. The patient complains of considerable headache, with nausea and prostration of strength. The eyes are somewhat suffused and the countenance flushed. The tongue is white and moist. The skin is at times moist and the temperature but little increased, at other times it is dry and the heat pungent. In some cases any increase in the velocity of the pulse is scarcely perceptible. There is commonly

constipation and loss of appetite. This is, for the most part, the appearance of the fever of the summer in its first attack. Gastric symptoms are seldom severe, the head being the organ most materially affected.""

In this paper Birt then summarised the data contained in the Army Medical Reports, and other sources. During the nineteenth century, phlebotomus fever had been included among the continued fevers (such as the enteric fevers and Malta fever), but in a number of Army reports, fevers of short duration had been segregated under the headings of simple continued fever, or febricula. From this study Birt proved that there was some milder infection contained in the Army figures for the continued fevers, in addition to the enteric and Malta fevers, and this infection was not abortive typhoid, aberrant Malta fever, or malaria. He then concluded -

"A survey of this historical evidence renders it clear that:-

(1) There have been outbreaks of a short fever every summer in Malta since the earliest military annals.

(2) This fever is specific, for immunity is afforded by a previous attack. With much monotony it is yearly recorded that the recent arrivals are the sufferers."

Birt, loc. cit., showed clearly that the fever presented a fairly definite clinical picture, and the date of appearance of the first cases of fever could be predicted yearly with reasonable accuracy. However, he remarked that the diagnosis of this fever might be far from a simple matter.

Taussig (1905) described the disease as occurring on the Adriatic coast, and accused sandflies as being the vectors.

McCarrison (1906) described the disease as a short term fever occurring in the Chitral in 1903. He gave a good clinical description of phlebotomus fever under the name of Chitral fever. He observed:-

(a) The presence of leucopenia with diminution of the polymorphonuclear leucocytes.

(b) It was the locality, and not the individual which was infectious.

(c) A stay of a few hours was enough to originate the fever.

He failed to induce the disease by painting the throats of healthy volunteers with pharyngeal mucus from cases as he thought the disease might be spread by dust. He also failed to reproduce the disease in healthy men by the inoculation of blood from patients, probably because he drew off the blood after the first 24 hours of the disease, or the native subjects he inoculated were immune. He remarked that the period of the outbreak corresponded in a striking manner with the appearance of phlebotomi. The fever did not occur when these were absent. He experimented unsuccessfully with the insects, mainly because of the great difficulty he found in keeping them alive in captivity.

Manson-Bahr (1945) and Birt (1910[3]) have directed attention to the fact that McCarrison was just on the verge of the discovery achieved by Doerr in 1908 that the fever was due to an infective agent transmitted by the phlebotomus.

In 1908, an Austrian military commission, consisting of Doerr, Franz and Taussig (1909), as a result of observations made in the provinces of Herzegovinia and Bosnia (now in Yugoslavia) described the disease in detail and proved that the infection was due to a filterable virus transmitted by a psychodid fly, known as Phlebotomus papatasii. They also showed that the virus was present in the patient's blood during the first 24 hours of the fever, but not at forty hours, or later.

R. Doerr, writing in 1909 in the monograph by Doerr, Franz and Taussig, "Das Pappatacifieber" (1909), gave the disease its modern name, the English equivalent being phlebotomus, or sandfly fever. In passing, it is noteworthy that phlebotomus fever is the only common disease which reveals the insect vector (i.e. class of Insecta) in the name of the fever. This indicates the comparatively recent clinical appreciation of the fever, and its removal from the obscurity of the continued fevers or pyrexias of uncertain origin.

In 1921, the Director of Medical Services for the Royal Air Force appointed a Commission to investigate the causation, prevention and treatment of sandfly fever (Whittingham 1922[1]). This measure was considered necessary owing to the high sickness rate from that disease during the previous year amongst R.A.F. personnel in the Middle East. Malta was chosen for the investigation because of its freedom from malaria and other tropical fevers. The medical members of this Commission, Whittingham and Rook, have described minutely the various stages in the life history of Phlebotomus. They have also written a paper on the prevention of sandfly fever (Whittingham and Rook 1923[1]) which has been the standard work up to the present time.

As fresh bacteriological knowledge with regard to the filterable viruses became available, the infecting agent was subjected to more detailed study. Shortt and others (1936 and 1938) have cultivated the virus on the chorio-allantoic membrane of the developing chicken-embryo and in tissue cultures, and have made a careful study of its properties. Their work has been confirmed by Russian workers (Demina and Levitanskaja 1940, Demina 1941[1]).

During the Second World War, a number of clinical accounts of epidemics of sandfly fever have been published, (Anderson, 1941; Sabin et al, 1944 [1 & 2]; Walker and Dods, 1941; Hallmann, 1943); also several epidemiological studies (Cullinan and Whittaker, 1943; Milne, 1945.) Since the work of Whittingham and Rook, little advance has been made with the preventive aspect of phlebotomus fever.

History of Phlebotomus Fever in the Royal Navy.

Sir William Burnett (Whittingham 1924) gave an account of what he called summer fever in naval personnel engaged in the blockade of Malta in 1799. His description of the fever (vide supra) showed that it was phlebotomus fever.

A study of the Statistical Reports of the Health of the Navy from 1856 gave the following information:-

1856 - 1909. As in the Army Reports (Birt 1910[1]) undiagnosed cases of sandfly fever were included under 'Simple Continued Fever' or 'Pyrexia of Uncertain Origin'.

In 1909, Kilroy allowed himself to be bitten by phlebotomi, and contracted the disease. Venous blood withdrawn from him on the first day of the fever was inoculated into a volunteer and reproduced the disease.

1910 - 1918. The Reports grouped short term fevers under the term Pyrexia, adding a note that many of the cases were probably "cases of phlebotomus infection."

Lambert (1918) stated that in 1916 there was an outbreak of the disease at Mudros East. He reported an outbreak which occurred at Mudros between May and August, 1917, and described the clinical picture of the infection as observed by him in a series of 237 cases.

The Report for 1919 stated that the majority of cases on the Mediterranean Station classed as pyrexia were probably cases of phlebotomus fever.

In the Report of 1923, an outbreak was described in the 11th Royal Marine Battalion at Constantinople; 164 cases occurred in this unit. This Report also stated that cases were regularly notified from ships refitting at Malta Dockyard.

Shaw (1929) gave the following table of incidence of the disease in the Navy:-

Sandfly Fever.

Year	Case Ratio per 1,000.
1921	0.47
1922	0.46
1923	2.49
1924	0.90
1925	0.72
1926	0.29

He also showed that the average yearly incidence on the Mediterranean Station of pyrexia of uncertain origin was:-

Period	Case Ratio per 1,000.
1897 - 99	41. 7
1907 - 09	9. 8
1925	2. 2

It would appear that the fall in cases diagnosed as pyrexia of uncertain origin was due to the more accurate recognition of cases of phlebotomus fever.

Table 1 has been compiled from the 'Health of the Navy' reports from 1930 till 1936, the latest one available. From 1936 onwards, the figures have been obtained from the Naval Health Officers' Annual Reports, for the Mediterranean Station.

Table 1.

Incidence of Phlebotomus Fever on the Mediterranean Station From 1930 to 1940, and Malta 1944 and 1945.

Year	Number of Cases	Case Ratio per 1,000 strength	
1930	39	0·52	
1931	-	2·51	
1932	-	4·94	
1933	-	2·75	
1934	-	2·80	
1935	33	1·58	
1936	158	6·38	
1937	70	3·95	
1938	47	2·60	
1939	41	--	
1940	63	--	
1941	-	--	
1942	-	--	
1943	-	--	
1944	2,795	349·36	X
1945	1,365	136·50	X

X Malta Shore Establishments only.

Note. Mediterranean Station.

In peacetime the Mediterranean Fleet is based at Malta, and naval personnel for the most part serve their commission in establishments on the island, or in ships which leave the harbours for exercises at specified intervals.

EPIDEMIOLOGY

Geographical Distribution.

The disease survives in those parts of the world where the climatic conditions are suitable for the vector to complete its life cycle. A long period of dry, hot weather, and suitable breeding grounds, are the main requirements of the sandfly. Especially in Europe, Africa and Asia, the disease is widespread in those parts which lie in the belt between 20° and 45° North latitude. Whittingham (1924) has stated that phlebotomus fever is endemic wherever Phlebotomus papatasii can breed. Manson-Bahr (1945) has pointed out that in Bermuda where the phlebotomus is absent, the fever is not found.

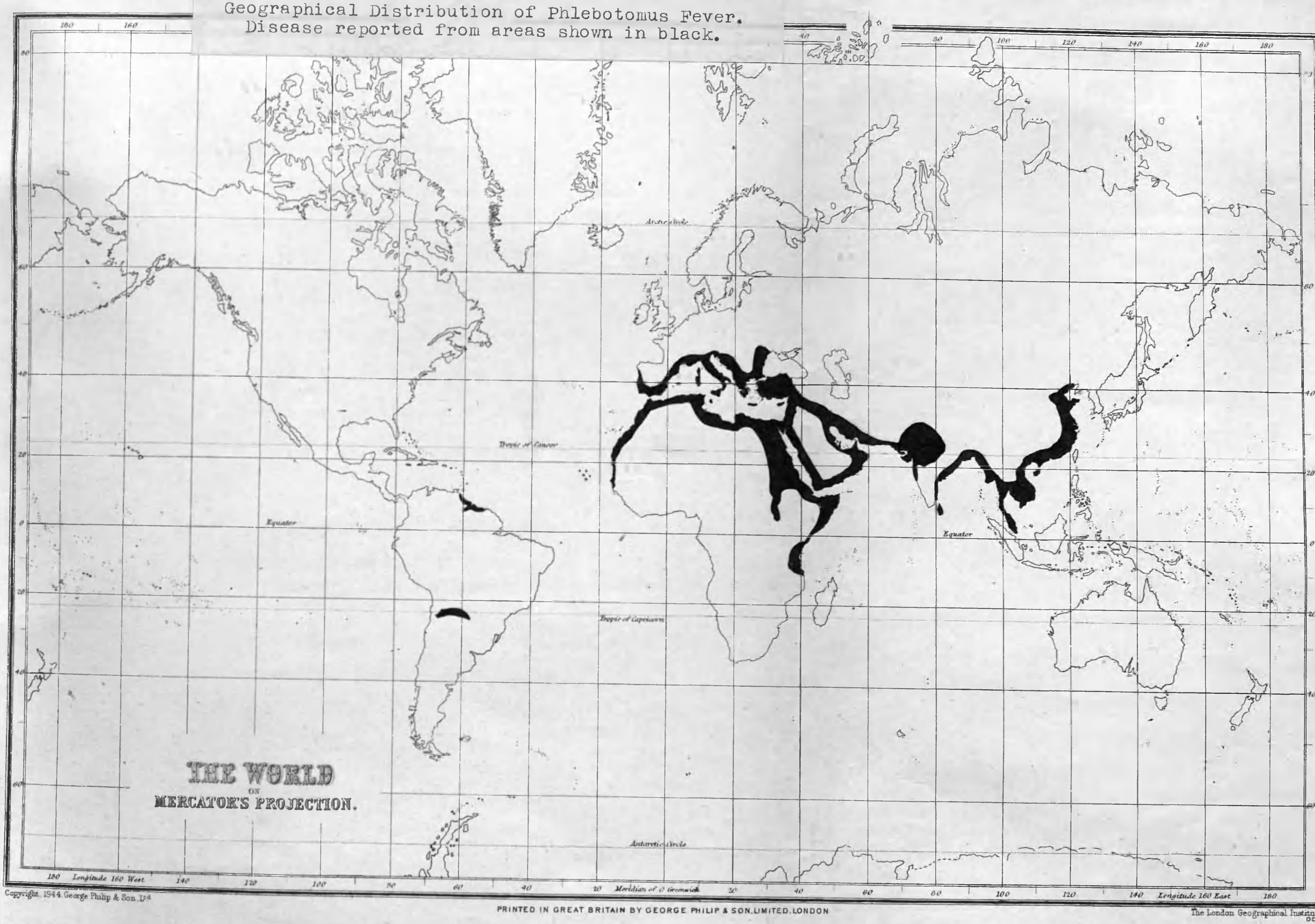
Outbreaks of the disease have been reported from the following regions, (Map 1).

Mediterranean Area.

The Atlantic Coast of Portugal, Gibraltar, Corsica and the Mediterranean Coast of France. In Italy the disease is definitely known as far North as the Po valley; Sicily (Ferguson 1943), Malta, along the Adriatic Coast of Yugoslavia as far North as the Istrian Peninsula, Greece (Hallmann 1943), Crete, Cyprus, Syria, Palestine (Walker and Dods 1941 and Milne 1945), Egypt (Philip et al. 1944) and the northern shores of Africa. Briefly, the disease is prevalent in the whole Mediterranean littoral, and particularly in the eastern part.

MAP 1.

Geographical Distribution of Phlebotomus Fever.
Disease reported from areas shown in black.



The U.S.S.R.

Crimea, Turkestan and Transcaucasian region, (Mrugowsky 1942).

Middle East.

(Bulmer 1943; Cullinan and Whittaker 1943), Iraq, Persia, Aden and Red Sea Coast of Arabia.

Africa.

Kenya, Tanganyika Territory and the Anglo-Egyptian Sudan.

India.

(Megaw and Gupta, 1927). The North West Frontier at Peshawar and Chitral, the Central Provinces, Northern Punjab, and in the region of Poona. Ceylon, and along the coast of the Bay of Bengal in Burma.

China.

The disease has been observed as far North as Peking and Tientsin, and as far South as Hong Kong.

South America.

Bolivar and Northern Argentina (Strong 1942).

The disease appears to persist chiefly, but not exclusively, in the low lands of these countries.
In India, Graham (1915) stated that the fever and phlebotomi were found up to a height of 7,000 feet, a figure re-quoted by Whittingham (1938). More recently, Strong (1942) and Manson-Bahr (1945) have stated that the disease is known up to a height of only 4,000 feet, but no reason can be found for this lower figure.

Seasonal Distribution and the Effect of Climatic Conditions on Sandfly Fever.

Whittingham and Rook (1923[2]) showed that Phlebotomus papatasii requires eight consecutive weeks with the mean daily temperature between 65° and 90° F., and an earth temperature (4 foot) of over 60° F. This temperature requirement, together with the necessity for sufficient moisture and organic debris for the fly to complete its life-cycle, explains the geographical distribution of the disease and its occurrence in the summer months.

Whittingham (1924) stated that in relatively dry areas, the disease was confined to the coast line, rivers or oases, that is proximity to water; or places where there was a marked drop in atmospheric temperature at night, and consequently a heavy fall of dew. He pointed out that in humid areas, such as Malta, there were two waves of fever which coincided with two broods of sandflies. This he believed to be because climatic conditions for the life-cycle of the fly were nearly optimal; whereas, in the less humid Bagdad area, there was only one wave of the fever and one brood of sandflies each season.

Whittingham (1924) also showed that infected sandflies failed to transmit the disease to human volunteers when the temperature fell to 54° F. This explains the delay in the appearance of the fever in years when the spring is cool, and the early appearance of cases if the warm weather comes early. A point well illustrated in the two epidemics studied in the present investigation (vide Graph 3).

Manson-Bahr (1945) whilst agreeing that the disease is mainly one of the summer and early autumn months in subtropical regions, remarks that in the tropics it may break out at any time as an epidemic amongst new arrivals.

Epidemic Tendency.

Whittingham (1924) stated that epidemics of phlebotomus fever occurred in endemic areas only when the adult fly was present, i.e. during the summer months.

Whittingham and Rook (1923[1] and 1923[2]) and Whittingham (1938) observed that there were usually two waves of the disease annually, each lasting three to four weeks, The first wave occurred at the beginning of the hot weather, and the second in the autumn, with a two months' lull between them, which corresponded to the time taken for P. papatasii to develop from egg to adult. They claimed that larvae that had weathered the winter hatched out early in the summer and caused the first wave of cases. The second brood, which hatched out about eight weeks later, was responsible for the second wave of infection.

The infectivity of the virus is high in susceptible individuals. Manson-Bahr (1945) stated that in phlebotomus-haunted places, as many as 70 per cent. of new-comers are attacked.

Rogers and Megaw (1939) state that the disease occurs in sharp explosive epidemics in which 90 per cent. of the population may be affected. But in many localities the fever is endemic and attacks chiefly new-comers from places where the disease does not occur. They also draw attention to the important fact that the disease varies much in severity in different outbreaks and in different localities.

Contingents of troops spending their first summer in an endemic area often experience an epidemic, whilst in subsequent years in the area only a few cases occur among the troops. This seasoning process is the result of active immunization, and may take the form of clinical sandfly fever or pass unnoticed as a subclinical infection. It is an important factor in determining whether an epidemic will occur among troops, the epidemic tendency being much greater among unseasoned (or 'unsalted') troops.

Favourable climatic conditions and the presence of suitable breeding grounds for phlebotomi play a large part in determining whether an epidemic will start, but further investigation is required to ascertain why epidemics suddenly start in one endemic area, and yet cause only a few cases in neighbouring areas. For example, in 1944 and 1945, few cases of sandfly fever occurred in the naval personnel in Tunisia, where both phlebotomus and fever are known, although movements of men between Malta and Tunisia were frequent. Before an epidemic can start, it is necessary to have large numbers of phlebotomi reaching the imaginal stage of development about the same time, a requirement which is greatly assisted by the presence of abundant rubble in close proximity to human habitations. It is generally agreed that the insects become infected in the breeding grounds (Whittingham and Rook 1923[2], and Young, Richmond and Brendish 1926).

Whittingham (1924) has stated that epidemics of the disease depended on :

(1) the number of infected phlebotomi.

(2) the number of susceptible people.

During the present investigation it was noted that periods of increased case incidence were accompanied by large numbers of phlebotomi. As a result the following view is put forward. In endemic areas, the majority of phlebotomi are infected, and if conditions are favourable to large numbers of insects reaching maturity then an epidemic is likely to occur, provided that susceptible individuals are available. Therefore, the first of Whittingham's governing factors stated above would require modification to :

(1a) Optimal breeding conditions allowing large numbers of infected phlebotomi to reach maturity.

The Virus.

The causal agent of phlebotomus fever is considered to be an ultra-microscopic filter-passing virus.

Doerr and his colleagues claimed that the infection was due to a filter-passing virus, and this was confirmed by Birt (1910[2]). Then Whittingham (1921 and 1922[1 & 2]), during his preliminary investigations in Malta, demonstrated a leptospira, morphologically resembling L. icterohaemorrhagiae in cases of suspected sandfly fever. He isolated the organism by blood cultures in Wenyon-Noguchi medium, and found that it differed from L. icterohaemorrhagiae in that it had no pathogenicity for guinea pigs.

At the same time, Couvy (1922), working in Beirut, also isolated a leptospira from cases of suspected sandfly fever. Whittingham's failure to confirm his earlier observations led him to doubt that a leptospira was the causal agent, (Whittingham 1924).

Kligler and Ashner (1928) in Palestine, in a series of careful experiments, failed to demonstrate any leptospira in infected human blood, or in sandflies caught in patients' houses. Infected human blood and emulsions of infected and uninfected sandflies were also examined by Poole and Sachs (1934) by dark ground illumination for the presence of spirochetes, but without success.

It is now generally agreed that the disease is due to a virus. Observers who found leptospira were possibly dealing with some mild variety of Weil's disease. In both diseases conjunctival congestion, frontal headache and pains in the limbs occur, and in Weil's disease non-icteric cases are now well recognised, (Harries and Mitman, 1944).

Properties of the Virus.

(a) Filterability.

Doerr (1908) proved that the causal agent of phlebotomus fever would pass through the pores of a Reichel earthenware filter. Birt (1910[3] and 1910[4]) filtered infective blood through a Chamberland F. candle, diluted it 1 : 9 in saline, and reproduced the disease with this filtrate in a volunteer. Graham (1915) used the Berkefeld filter and Kligler and Ashner (1928) the Berkefeld N candle; they found the resulting filtrates infective to susceptible individuals. Shortt, Poole and Stephens (1934[1 and 2]) filtered citrated whole blood and citrated-glycerinated blood through Chamberland L 3 and L 5 candles, and infected human volunteers by inoculation with the filtrates. They also produced a febrile reaction in Macacus rhesus monkeys with human blood which had been passed through a Chamberland L 13 bougie.

Sabin et al (1944[1]) carried out Gradocol (collodion) membrane filtration tests, and found that the virus passed with ease through membranes having an average pore-diameter of 200 millimicrons or more.

(b) <u>Size.</u>

Shortt, Pandit and Rao (1938) using virus grown on the chorio-allantoic membrane of the developing chick, carried out filtration tests with gradocol membranes. They found that the virus whilst retained by a membrane having an average pore-diameter of 380 millimicrons could pass through a membrane with an average pore-diameter of 480 millimicrons.

Sabin et al. (1944[1]) also carried out gradocol filtration tests, and found the virus to be of small size, much smaller than the figures quoted above. They used serum from cases of the fever, and found that the virus passed with ease through all membranes having an average pore-diameter of 200 millimicrons or more. Passage through the 100 millimicron average pore-diameter membrane was probable but questionable, since the filtrate did not reproduce the disease, although two of the four human subjects used in the test were immune to subsequent inoculation with active virus. Neither disease nor immunity followed the inoculation of filtrates from the 75 or 50 average pore-diameter membranes. These workers applied Elford's formula (which estimates the size of the particle) to their findings, and stated that the virus was certainly not larger than 40 to 60 millimicrons, and probably not larger than 25 to 37 millimicrons. They have suggested that it is not improbable that the true size of the phlebotomus fever virus may be even smaller than the above estimated sizes, and perhaps falls in the same range of magnitude as the virus of yellow fever, which is 22 millimicrons.

(c) Resistance to Physical and Chemical Reagents and Preservation.

Birt (1910[1]) found that the virus retained its activity for a week in vitro, at temperatures of 20° F. to 80° F. Lépine (1927) showed that the virus was killed by heating to 55° C. for ten minutes. Shortt, Poole and

Stephens (1934 [1 and 2]) used with success 2 per cent. sodium citrate and 50 per cent. glycerol as preservatives, singly and mixed together, for their specimens of infective blood, which had to travel from Peshawar to Kasauli, a journey of some twenty-four hours in the summer heat of India. The same workers (Shortt, Poole and Stephens, 1934[1] and 1935[2]) have also shown that the virus is resistant to drying. They desiccated infected sera over sulphuric acid in vacuo, and inoculated the product of 1 cc of serum dissolved in 3 cc of normal saline into two volunteers. This produced a typical attack of phlebotomus fever in one of them.

Sabin et al. (1944[1]) preserved the virus in serum for six months in the frozen state by storage at a low temperature produced by solid carbon dioxide. They also kept for the same period specimens of infective serum in the lyophilized state, and found them capable of reproducing the disease. (Lyophilization is a special method of dehydration of serum by rapid freezing and drying under high vacuum pressure).

(d) General Properties.

The original studies of Doerr and his co-workers (1909) and later frequently confirmed (Birt 1910[1], Whittingham 1924, and others) established that the serum obtained during the first twenty-four hours of the fever, but not at forty hours or later, could reproduce the disease in human beings.

Moshkovsky and his associates (1936) demonstrated that the virus may be present in the blood one or two days before the onset of fever. Sabin and his co-workers (1944[1]), as a result of their experiments, found that:

(i) Serum obtained from spontaneous cases occurring among troops in the Middle East and Sicily regularly reproduced the disease in human volunteers.

(ii) By means of the intracutaneous and intravenous routes of inoculation, approximately 95 per cent. of over 100 human adults were found to be susceptible, regardless of sex or colour. Doses of the virus (i.e. infected serum) which produced the disease by the above routes failed to produce the disease in 50 to 75 per cent. of individuals when injected subcutaneously or intramuscularly.

(iii) No virus was demonstrated in the cerebrospinal fluid obtained on the first or second days of the experimentally reproduced disease, even when large amounts (2 cc intracutaneously, and 15 cc intravenously) of the cerebrospinal fluid were inoculated.

(iv) In the experimentally reproduced disease the virus was found in the blood at least 24 hours before the onset of the fever and during the first 24 hours of the fever, but was no longer demonstrable 48 hours after the onset.

(v) Passage of the virus seven times by inoculation into human beings caused no apparent change in its properties.

(vi) Two strains of the virus, one isolated in the Middle East, and the other in Sicily, were proved to be immunologically identical.

(vii) Virus irradiated with ultraviolet light has been found capable of producing immunity without giving rise to the disease.

(e) Cultivation.

Shortt, Rao and Swaminath (1936) employed the original method devised by Woodruff and Goodpasture (1931) for the cultivation of the sandfly fever virus on the chorio-allantoic membrane of the embryo-chick. The same technique as that used for their work with the vaccinia virus (Rao, Pandit and Shortt 1936) was adopted. The Inoculum consisted of pooled fresh liquid serum from four different cases of sandfly fever, or else dried serum. The eggs were incubated at 39^{o} C. and examined at intervals of four days for the presence of lesions on the chorio-allantoic membrane. In 'positive' preparations a characteristic reaction was produced, which took the form of an opaque patch measuring about 10 mm. in diameter. Microscopically the lesion consisted of proliferation, necrosis and desquamation of the ectodermal cells, causing the formation of a minute ulcer; together with proliferation of the entodermal cells. Shortt et al., have not used the term inclusion bodies, but have preferred inclusion material instead as the cytoplasm of many cells appeared to have been wholly replaced by red-staining (in sections stained with Giemsa's or Mann's stains) inclusion material, and no characteristic inclusion bodies could be detected.

Demina and Levitanskaja (1940) confirmed this work and proved that inoculations of emulsions made from infected chick-embryos produced symptoms of typical phlebotomus fever in human volunteers.

Demina (1941[1]) showed that the virus tended to lose its virulence and antigenic properties by repeated passage in the chick-embryo.

Demina (1941[2]) in the course of investigations on the attenuation of the sandfly fever virus for immunization purposes proved that the virus was inactivated in virulent serum by treatment with 1 : 1000 formalin, or by drying in vacuo over sulphuric acid in the presence of acetone or phosphates. Attempts to absorb the virus from serum at p H 6·8 - 6·9 with aluminium hydroxide and kaolin were unsuccessful.

Shortt, Pandit and Rao (1938) claimed to have cultivated the virus in tissue cultures of finely minced 10-day-old chick-embryo in Tyrode's solution. They also showed that the proof of cultivation of the sandfly fever virus in the chick-embryo, depended not only on the production of focal lesions in the chorio-allantoic membrane, but that the serum of patients convalescent from sandfly fever was able to neutralise the lesion producing agent in the egg-membrane. Of six convalescent sera tested, all but one inhibited growth of the virus on the membrane.

The controls with normal serum all showed growth of the virus, while the convalescent sera themselves gave no growth.

(f) Pathogenicity to Man and Animals.

For practical purposes man alone suffers from sandfly fever. Many attempts have been made to transmit the infection to animals by the inoculation of blood or serum obtained from a case of sandfly fever in the first 24 hours of the fever.

Doerr and Russ (1909) failed to infect laboratory animals. They then mixed some animal serum with some known infective serum and inoculated the mixture into a human volunteer and produced the clinical picture of sandfly fever, which proved that the animal serum had no neutralising properties. Birt (1910[2]) also found that the virus was not pathogenic to laboratory animals.

Poole and Sachs (1934) inoculated guinea pigs and rabbits with human blood from sandfly fever patients, and also emulsions of infected and uninfected sandflies, but without effect.

Shortt, Poole and Stephens (1934[1] and 1935[2]) have shown that the virus is feebly pathogenic to the Macacus rhesus monkey, and that inoculation of two human volunteers with 5 cc of infected monkey blood reproduced symptoms resembling a mild attack of phlebotomus fever. Human controls inoculated with uninfected monkey blood showed no reaction.

Sabin and his associates (1944[1]) tested the pathogenicity of the virus by inoculation of serum or blood of proved infectivity for human beings by intracerebral, intracutaneous, subcutaneous, intratesticular, intraperitoneal or intranasal routes in a large number of lower animals, consisting of the usual laboratory animals, several species of monkeys (including M. rhesus), wild rodents and other small 'vermin' commonly found along the North African shores. No evidence of pathogenicity was obtained in any of the animals.

The Vector.

Phlebotomus papatasii, a midge measuring about 3 mm. in length, has been proved to be the true carrier of this disease.

The insect was first described by Rondani in 1840 (Marett 1910), and later studied by Grassi (1907), who believed that the development of the phlebotomus ovum took place in drains, or in close relationship to sewage, similar to that harmless member of the same family Psychoda phalaenoides. Grassi observed several stages of the life history of the insect in a damp cellar in Rome.

Howlett (1909) observed the larval development from ova, in India.

Marett (1910), who set out to find some means whereby sandflies could be reduced in numbers, made the important discovery of the breeding grounds of the phlebotomus. He drew attention to the relationship between rubble and sandflies.

He trapped a garden wall built of loose stones in the Maltese style (similar to the drystone dykes of Scotland) and found large numbers of phlebotomi. The insects appeared between 10 and 11 o'clock at night, but were not seen in daylight.

He investigated the loose rubble at base of some old fortifications, and found phlebotomus larvae "where it was damp and cool". Marett (1913 and 1915) confirmed his earlier findings, and observed most of the stages in the development of the phlebotomus. He succeeded in breeding phlebotomi in the laboratory, and would appear to be the first worker to do this, although the credit is usually given to Whittingham and Rook, who reported their results in 1922.

Whittingham and Rook (1922 and 1923[2]) achieved success by paying special attention to the conditions of temperature, humidity, and food supply; and getting conditions in the breeding cages as near as possible to those of the sandfly breeding grounds in nature.

Life History. (Figures 1 and 2).

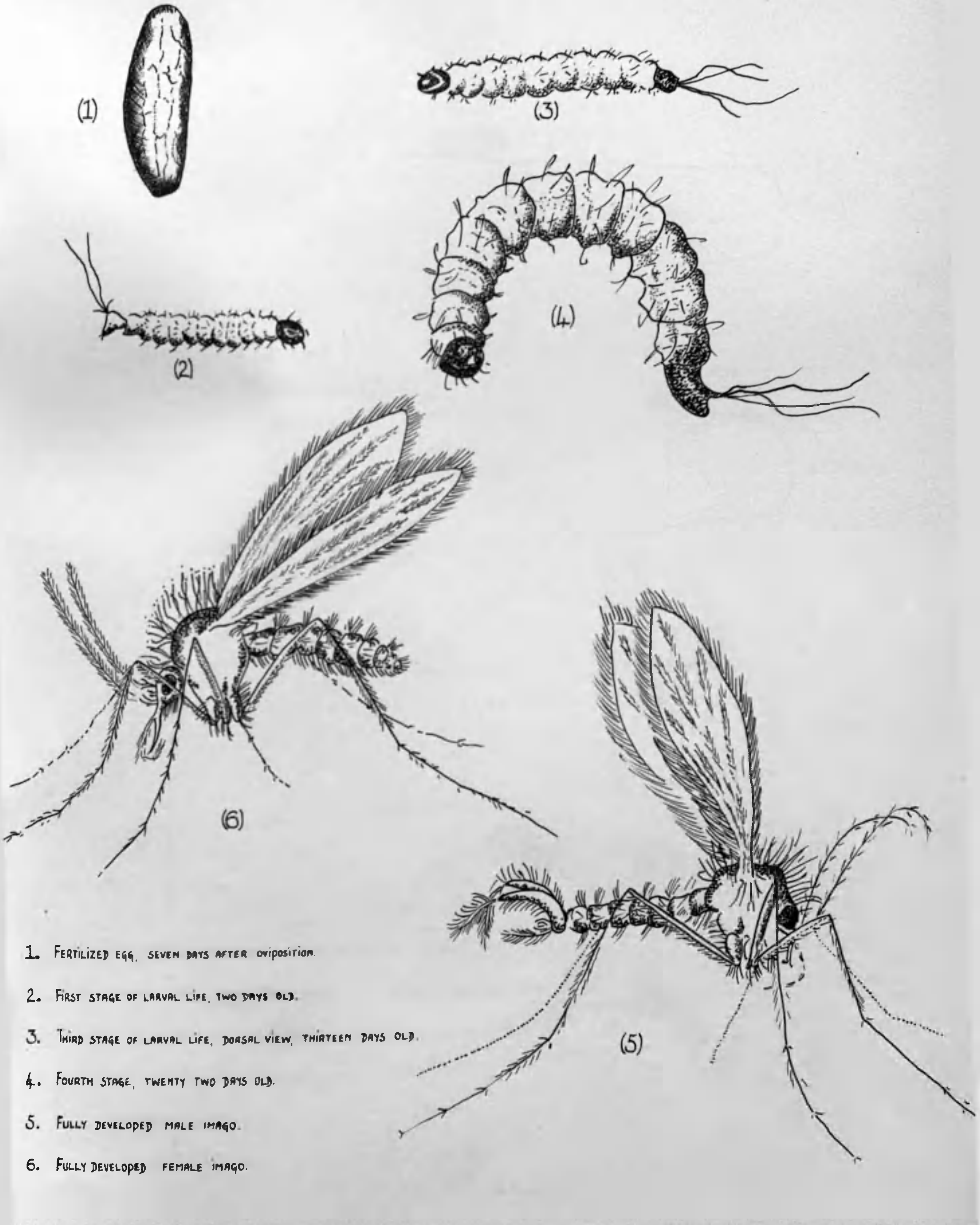
The following is a summary of the life history of P. papatasii based on the comprehensive observations of Whittingham and Rook (1923[1] and 1923[2]) and Whittingham (1923).

Imago.

The newly hatched phlebotomus is snowy white, except the eyes, which are black. The body and wings are densely covered with hairs. The wings are moist, crumpled and held horizontally over the body. They

Figure 1.

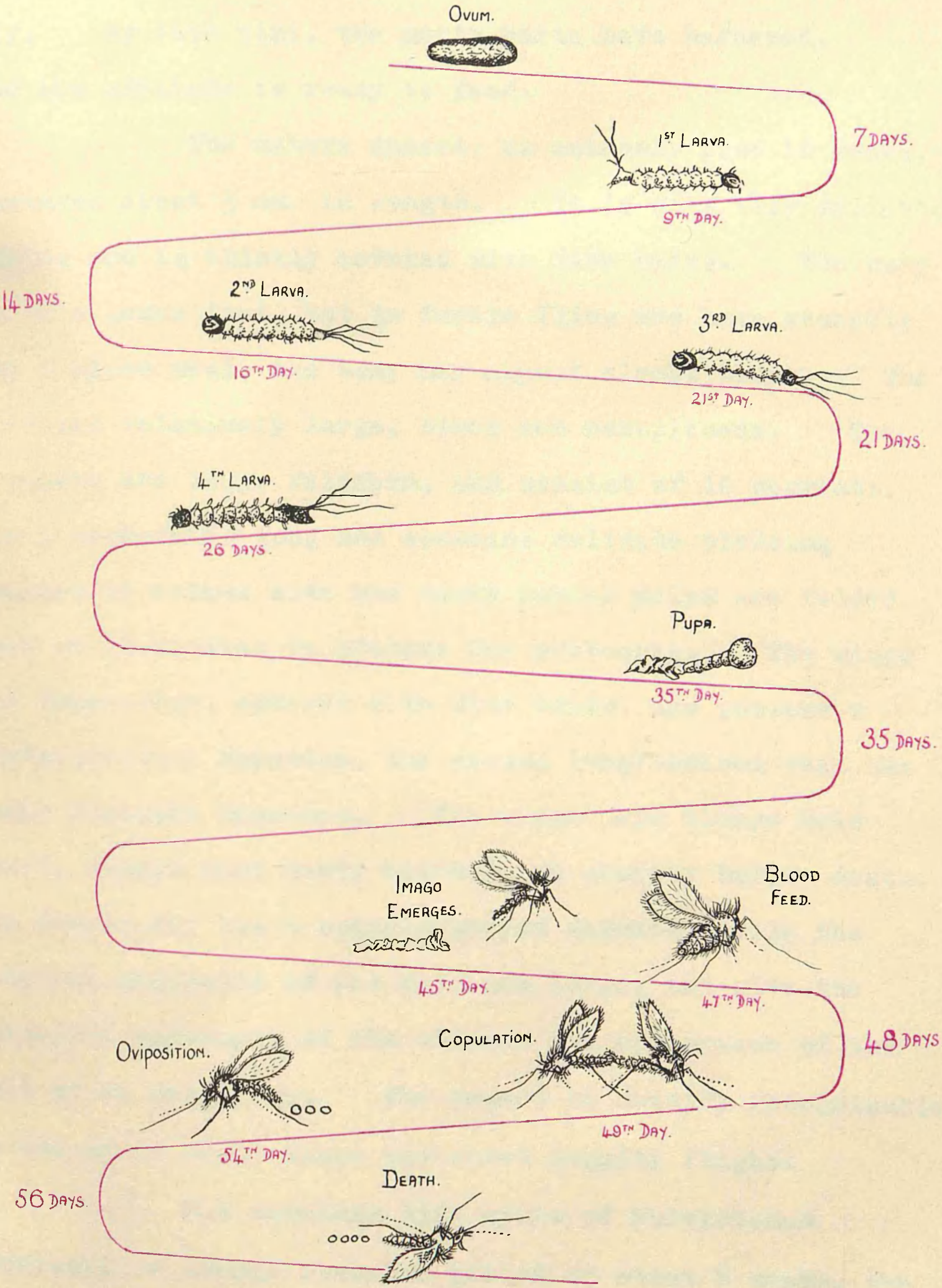
TO ILLUSTRATE LIFE HISTORY OF PHLEBOTOMUS PAPATASII.
(after WHITTINGHAM).



1. FERTILIZED EGG, SEVEN DAYS AFTER oviposition.
2. FIRST STAGE OF LARVAL LIFE, TWO DAYS OLD.
3. THIRD STAGE OF LARVAL LIFE, DORSAL VIEW, THIRTEEN DAYS OLD.
4. FOURTH STAGE, TWENTY TWO DAYS OLD.
5. FULLY DEVELOPED MALE IMAGO.
6. FULLY DEVELOPED FEMALE IMAGO.

Figure 2.

DIAGRAM OF LIFE HISTORY OF PHLEBOTOMUS PAPATASII.



DURATION 8 WEEKS.

do not dry and unfold until the atmospheric humidity decreases; this usually occurs within three hours after dawn. When the wings are dry, they are raised to an angle of 45° above the body, and the insect is able to fly. By this time, the mouth parts have hardened, and the creature is ready to feed.

The mature insect, as commonly seen in rooms, measures about 3 mm. in length. It is of a very delicate build, and is thickly covered with fine hairs. The body is of a lemon tint, but in female flies who have recently had a blood meal, the body may appear almost black. The eyes are relatively large, black and conspicuous. The antennae are long, filiform, and consist of 16 segments. The proboscis is long and contains delicate piercing organs; on either side the bushy labial palps are folded back on themselves to protect the proboscis. The wings are lanceolate, covered with fine hairs, and possess a characteristic venation, the second longitudinal vein has three distinct branches. The wings are always held erect, except when newly hatched and shortly before death. The female fly has a spindle shaped abdomen, while the external genitalia of the male are large, and give the posterior extremity of the abdomen the appearance of the tail of an aeroplane. The insect is readily recognisable by its small erect wings and short hopping flight.

The complete life cycle of Phlebotomus papatasii in summer covers a period of about 8 weeks, the exact time depending on the food supply, temperature and humidity. In Malta, the ovum stage lasts about 9 days; the larval stage about 28 days; the pupal stage about 10 days, and the imago stage about 14 days.(Fig. 2). Young, Richmond and Brendish (1926) found that the average duration of the various stages of the life history in Peshawar during the summer were, egg to larva 11.6 days, larva to pupa 21·1 days, pupa to adult 6·7 days and egg to adult 39·1 days.

The Ovum measures approximately - length 0·385 mm, breadth 0·12 mm. It is ovoid in outline, somewhat convex dorsally, and flattened or slightly concave ventrally. At first it is glistening and pale yellow; but after 24 hours the shell becomes brown, darkens daily and surface markings appear. These take the form of longitudinal dark ridges, which are intersected at intervals by cross ridges.

About the ninth day, the embryo with its caudal bristles which appear as two black lines, can be seen through the distended egg shell. The egg shell is ruptured in the dorso-anterior region by the action of the egg tooth on the head of the larva, and the little creature emerges. A high humidity is necessary for hatching, which usually takes place in nature between midnight and dawn.

Larva. When newly hatched, the larva is white, moist and glistening except for the brown mouth parts, egg tooth and caudal bristles. At this stage (the beginning of the first instar), the caudal bristles lie along the ventral surface. As the larva dries, the colour changes to grey, and the caudal bristles rise to an angle of 45°. The head becomes black, except for a Y-shaped area on the dorsum. About an hour after birth, the larva starts to feed greedily.

The larva has a head and twelve body segments. There are no eyes. The head is furnished with strong jaws, consisting of two mandibles dorsally, and a single ventral labial plate. There are a few hairs on the body, and on the head a pair of small antennae.

After feeding voraciously for five days, on the sixth day the bloated little creature becomes sluggish, stops feeding, and the gut is emptied. On the seventh day usually, the first moult occurs, and the second instar begins. The old skin is shed by the larva tapping the ground with its head, the line of cleavage being at the base of the head segment. There are four instars, and the differences in the larvae are briefly shown in the following table:-

Table 2.

Stages of Larval Life.

Table showing the Duration and Appearance of Larvae during the various stages of Larval Life, (after Whittingham & Rook).

Instar	Days of Larval Life	Distinguishing Features of the Larvae.
First	1 to 7	Single pair of caudal bristles and presence of egg tooth.
Second	7 to 12	2 pairs of caudal bristles, slight pigmentation of distal part of last segment.
Third	12 to 17	2 pairs of caudal bristles, brown pigmentation of whole of last body segment.
Fourth	17 to 26	2 pairs of caudal bristles, brown pigmentation of last segment and central part of penultimate segment.

In the 28th days of larval life, the grub grows from 0·46 mm. to 3·78 mm. in length.

The insect passes the winter months in the fourth larval stage and is fairly resistent to drying and moisture.

At the conclusion of the fourth moult, pupation occurs. The duration of the time between the hatching of the ovum and pupation may be as short as 24 days, or as long as 202 days. The latter figure refers to hibernation which occurs in the fourth larval stage. The earth temperature (4 foot) of below 65° F. retards pupation. When about to pupate, the larva seeks a fairly dry spot, e.g., the under-surface of a stone. It then becomes very sluggish, and in due course the pupa just emerges, and no more, from the anterior end of the larval skin. The cast-off skin becomes crumpled and remains round the terminal segments of the pupa like a wrinkled stocking.

The Pupa measures about 3 mm. in length, and is roughly club-shaped. The developing eyes and antennae can be seen through the pupal case.

The imago emerges at night when the humidity is high by a rupture of the pupal case in the region of the cephalo-thoracic junction.

Feeding. Only the female phlebotomus bites. A feed of blood is essential for the eggs to become fertilised. The insect usually bites after sunset, unless, as a result of strong winds which may keep the sandflies in the breeding grounds, the insects are driven to seek food by hunger, and will then bite by day. Man is usually bitten on the exposed skin, but the insect will also bite through a thin sock.

The phlebotomus alights with wings erect and body parallel to, but raised off the skin on which it rests. In this attitude, the fly may make short runs over the skin, apparently seeking a suitable spot. The fly steadies itself, then quickly lowers its body by sudden spreading out of the legs; there is very little tilting forward of the body. The proboscis is inserted into the skin for half to two-thirds of its length. The actual bite is not felt, the pricking sensation is caused by the saliva, and takes place a few seconds later. The saliva delays clotting of the blood. Within ten seconds of starting to feed the blood appears in the stomach, and after two and a half minutes, this organ is so distended that it almost fills the abdomen. The abdomen is bent downwards so that the posterior end almost touches the skin surface. The proboscis is withdrawn, and the insect flies away to a low part of the room. Complete digestion of the meal takes five days in a pregnant, and longer in a non-pregnant, fly.

In a later paper, Whittingham (1924) showed that the female P. papatasii lives for 10 to 14 days, during which some feed daily, but most flies only every three or four days. The time taken for a blood feed by a previously unfed fly is about two minutes, and five to ten minutes by one which has fed previously, especially if pregnant.

Young, Richmond and Brandish (1926) maintained that in nature the female phlebotomus usually feeds only once, and is fertilised during the first 36 hours of adult life. After a blood meal, the insect remains indoors for 60 to 84 hours, then returns to the breeding grounds, lays its eggs within 108 hours, and may repeat the process of feeding and oviposition a second time.

Copulation. This usually takes place about the second day of adult life. In the majority (96 per cent.) of cases, the female has had a blood meal prior to the act. The course of events is usually that the female, having had a feed of blood on the first day, has partly digested it twenty-four hours later, and mounts to the higher parts of the room. There the males congregate, awaiting the females. Phlebotomi, except in copulation, will be found with their heads pointing upwards on a wall. The male approaches the female from behind, swings round his body and grasps the posterior extremity of the female in his claspers. Copulation takes about thirty minutes, and once is sufficient to fertilise most of the eggs in the female. The duration of pregnancy is 7 to 10 days; further feeds of blood may be taken, but are not necessary to the development of the eggs. Oviposition occurs on the ninth or tenth day, the fly usually dying in the process on the fourteenth day of adult life. The full complement of eggs in the ovary is about forty, but generally they are not all laid.

Habitat. Phlebotomi seek a dark sheltered spot where there is nitrogenous matter and a moderate degree of humidity to lay their eggs. They breed in rubble, in cracks in embankments, walls and buildings, especially at their bases, in sun cracks in the ground, and cultivated soil. Phlebotomi have been observed ovipositing on mosquito nets and in clothes during the humid summer weather in Malta.

Young, Richmond and Brendish (1926) found that material in which sandflies could breed had just to be sufficiently damp to cohere to the finger and thumb when rubbed between them. The material was too dry if it powdered to dust on rubbing and too wet if it stuck readily.

Smith, Mukerjee and Lal (1936) in India confirmed Whittingham and Rook's observations and found that the insects passed through the winter in the larval stage, and that breeding was encouraged by darkness, moisture and traces of organic matter. They found that a favourite breeding place for sandflies was the cracks and crevices in the walls of dilapidated latrines.

The insects have also been shown to breed in holes in trees (Gabbi, 1915) and recently McArthur (1942) remarked that the insects may be carried in timber or other cargoes from place to place in ships, a matter of some importance in encampments where wooden hospital huts, latrines or other wooden structures are being erected.

Movements. The larvae move about like caterpillars, but do not wander far from their birthplace; they live in darkness and have no eyes. The pupa is only able to make slight backward and forward flicks.

The imago progresses by a short hopping flight, the distance of a single flight being about four yards. The insect seldom travels more than fifty yards from its breeding haunts during its whole life. This knowledge is important in connection with the prevention of phlebotomus fever.

The insects rest by day in their breeding places or on the walls of rooms, and are active by night. They enter rooms by any of the openings, windows, doors, ventilators or cracks. The females remain low in quest of a blood meal, but the males go to the higher levels to await the females. The flight of the insects is feeble, and they avoid all air currents, whether natural or artificial. As upstairs rooms are more exposed to air currents, they are less infested with phlebotomi than those on the ground floor. (Whittingham and Rook 1923[1]).

__Food.__ Food during the larval stages consists of nitrogenous material, such as the dead bodies of insects, lizards faeces and other organic materials, which commonly collect at the bases of walls. Moisture is also required, and this collects also at the bases of walls. The male imago feeds on organic matter. The female can feed on organic matter, but requires a blood feed to become pregnant.

__Temperature and Humidity.__ A high degree of humidity is required for all stages of the life cycle, except during hibernation in the larval stage. The adult fly would seem to prefer a relatively dry atmosphere.

The insect has definite temperature requirements. It hibernates in the fourth larval stage when the earth temperature (4 foot) falls below 65° F. A temperature of over 90° F. is injurious to the adult. The optimum temperature for all stages is 70° F. to 80° F.

__Attraction.__ Phlebotomus is attracted by human odour. This important fact was first observed by Birt (1910[2]), who stated that many insects were to be found in an inhabited room in dark corners away from the light, whilst none were found in the vacant room next door.

Whittingham and Rook (1923[1]) confirmed this by observing that sandflies accumulated in large numbers in the huts of the Maltese other ranks, which were closed up every second week-end whilst the men were on leave. The human odours from their clothes and bedding grew stronger as the windows and doors were closed in the temporarily unoccupied huts.

Whittingham and Rook (1923[2]) completed their paper thus:-

"Phlebotomus papatasii is directly responsible for the conveyance of phlebotomus fever to man. Prophylactic measures against this fever must be directed against the fly. It is only by having a sound working knowledge of the life history and bionomics of this insect that these measures can be applied successfully and economically."

Other Members of Phlebotominae.

As most of the work has been done on P. papatasii, very little is known about other species of the Phlebotominae, which might be vectors of the fever. The existence of the insects in proximity to patients has led observers to accuse P. perniciosus (Newstead 1911). P. minutus has been reported as the host in Aden (Strong 1942). P. sargenti, and P. caucasicus, and P. argentipes, have also been implicated. Such conclusions have been based on circumstantial evidence, and not upon experimental facts, and, therefore, must be accepted with reserve.

Other Insects as Vectors.

Doerr and his co-workers (1909) tested the bedbug (Cimex lectularius) and found that it did not transmit the fever. Sabin et al. (1944[1]) carried out controlled tests with mosquitos (Culex pipiens and Aedes aegypti) and human fleas (Pulex irritans). They showed that these insects were unable to transmit the disease. The negative results with Aedes aegypti are of special interest since this mosquito is the vector of the virus infections yellow fever and dengue. These diseases, especially the latter, have many features in common with phlebotomus fever.

The Flight of Phlebotomus.

Earlier observers had noted the short distances of flight (Marett 1913) and rapid side movements of the insect in flight (Birt 1910[2]).

Whittingham and Rook (1923[2]) stated:-

"The adult phlebotomus, when hatched, can only crawl. Later, when the wings are dry, it progresses by a short hopping flight, usually to one side or other. The distance of a single flight is never more than four yards, and it does not travel more than fifty yards from its breeding haunts, probably less. This knowledge is important in connexion with prophylaxis."

Sabin et al. (1944[1]), reviewing the literature on this point, concluded:-

"There is reason to believe that their range of flight is very short, and that insects found in human habitations probably originate from breeding sites within a radius of about 50 yards; there is some question, however, as to whether there may be some exceptions to this rule."

Whittingham and Rook (1923[2]) also showed that the insect rests by day in some dark corner where there is little air movement, or returns to the breeding grounds. It is active by night, but its flight is so feeble that air currents, whether natural or artificial, are avoided.

The insects, in nature, rarely fly higher than 10 feet above ground level. Owing to their delicacy, they abhor air currents, and require still atmospheric conditions for flight. Whittingham and Rook (1923[1]) made a careful study of the effects of air currents on phlebotomi, and found that there was a definite relationship between the force of the wind, and the number of flies found indoors. Roughly speaking, the flies were present in huts in inverse proportion to the force of the wind. A force four (Beaufort scale) wind, blowing for two or three consecutive days, cleared the phlebotomi from the huts on the windward side of the R.A.F. Station at Calafrana, and in the huts on the leeward side there was a considerable reduction in the numbers of phlebotomi.

They proved that artificial air currents, produced by means of fans, greatly reduced the numbers of insects indoors, and that this was a useful means of protection.

Personal Observations.

During May and June, 1945, a number of observations on the behaviour of phlebotomi were made in the R.N. Hospital, Malta, with a view to ascertaining the best means of using the DDT insecticide liquid.

(a) The insects were generally more prevalent in the lower floors of buildings. However, in the Sick Officers' Block, which was on the top floor of the Surgical Block, and about 40 feet above the ground level, there was a fairly heavy infestation of phlebotomi. It was found that the insects were breeding in considerable numbers in the sheltered ends of the verandahs, where the walls were cracked and provided good breeding sites.

(b) The flight was confirmed to be short and jerky, with side to side movements; prior to alighting on a human being, the insect was frequently observed to hover over its victim for several seconds.

(c) The insects rarely attacked persons in motion, and whilst feeding, flew away if disturbed by muscular contraction. This was tested repeatedly by sitting at an open window and leaning the bare fore-arm on the sill. When a sandfly landed and started to feed, slight movement of the forearm muscles caused it to fly away.

Further proof of this was obtained by observations on the nursing staff. The Night Duty Sisters, who, as a result of the number of cases to be given Penicillin, were constantly going from ward to ward in the open, were bitten much less than the Night Nurses, who, when not busy, sat at duty tables in the middle of the wards. During the early months of 1945, the Night Nurses were bitten so badly on the legs that it was being considered whether they should not, for protection of their legs against bites, wear white drill long trousers.

(d) The insects were never observed to fly straight into a room and attempt to bite an individual. They usually alighted round the window region, where they rested for some time before proceeding to some secluded spot within the room. The flies moved in a room by hopping flights along the walls or from one piece of furniture to another.

<u>The Bite of Phlebotomus.</u>

The virus inoculated by one infected phlebotomus is capable of inducing the fever in a susceptible individual (Birt 1915), but the bites of numerous infected phlebotomi fail to cause the disease in some people who appear to be naturally immune to this disease (Whittingham and Rook 1923[1] and Whittingham 1938).

Manson-Bahr (1945) states that the bites of the sandfly occasion a considerable amount of irritation, resulting in hyperaemia and even oedema.

Sabin and his associates (1944[1]) have recorded their observations on the bite of the phlebotomus, thus:-

> "While the bite itself is usually painful, there is no reaction to it until and unless the person has developed an allergy to the secretions deposited during the bite. In persons not previously bitten by these insects there is neither pain nor local irritation after the initial stab. The bitten site may be marked by a pinpoint, reddish or haemorrhagic spot, or may be inconspicuous. However, about one to two weeks later

(without exposure to other bites during the period) inflamed papules usually appear at practically all the sites of the original bites. These papules are 2 to 3 mm. in diameter, raised about 0·5 mm., pink or red, and not infrequently vesicular. Their appearance is not necessarily associated with itching, although moderate to severe itching is usually present later. These lesions are prominent for four to five days, and then slowly disappear. Once sensatization is established, such papules appear earlier after subsequent bites, and in certain hyper-sensitive persons, there is an almost immediate urticarial reaction which may produce pronounced and extensive swelling of the eyelids or lips when these sites are bitten. Some persons, however, do not become sensitive."

Personal Observations.

During the 1945 epidemic, many sandfly bites were examined in healthy persons, in cases of phlebotomus fever and in cases suffering from other diseases. The following points were noted.

(a) The act of biting was painless, but slight pain and itching appeared shortly after the phlebotomus had flown away. After some hours a weal appeared in the area around the bite.

(b) Sandfly bites, though generally on the exposed parts, were not invariably found there. Several persons were bitten on the upper abdomen and chest, though wearing pyjamas. During the warmest weeks of the summer, patients were bitten on the feet, especially on the tip of the great toe - the patients slept covered only by one sheet for coolness, and the phlebotomi must have bitten them through this.

(c) The insects appeared to show a preference for biting certain parts of the body. Favourite sites were eyelids, lips, pinna of the ear, palmar surface of the hands, forearms and bare legs.

(d) Individuals varied widely in their susceptibility to bites. In many persons, the bites caused little more than a transitory itching, whilst in others who were allergic to the salivary secretions, the bites caused considerable swelling and irritation. Several persons were seen in whom the vesicles containing blood stained fluid were produced. The itching from bites in sensitive persons was intense, and the oedema and itching took up to a week to subside.

The process of sensitization as described by Sabin et al. (1944[1]) appeared to be the most frequent sequence of events.

(e) Individuals who had lived more than a year in a sandfly area appeared to be less affected by the bites than newcomers. Of the Maltese questioned and examined, not one showed more than a very slight reaction to the bites of these insects. This suggests that, in time, desensitization occurs.

The above observations are in agreement with those expressed by Whittingham (1938), who stated that the immediate result was a weal at the site of the bite, which might take twelve to twenty-four hours to appear and several days to disappear in newcomers. Those who had been bitten repeatedly acquired an immunity to the insect's saliva, so that the weals appeared and disappeared within a few hours.

Three cases were seen in which the sandfly bites had caused a condition which fitted the description of 'Harara'. 'Harara' (i.e. Heat) is a skin condition produced by repeated bites and pruritis following the attacks of sandflies. It is commonly seen among newcomers to Palestine, and takes the form of an urticarial skin eruption confined to the face, arms and legs. Small vesicles and papules about 7 mm. in size develop in due course, and these become filled with clear or blood stained fluid. The itching and swelling associated with this condition is often considerable.

Cycle of Infection and Reservoir of Virus.

According to the present state of our knowledge, the disease is maintained by passage from man to man through the medium of the intermediate host and vector Phlebotomus papatasii. Secondly, cases do not arise by contact when the vector is absent. It is known that the virus disappears quickly from the peripheral blood of human beings. Recently, however, it has been stated (Manson-Bahr 1945) that the presence of the virus has been demonstrated in the blood by egg culture up to three to four weeks after the onset of fever. There is no evidence that any lower animals carry the virus. In endemic regions the native population are immunised against the disease by one or more attacks of the fever in childhood, and frequent subclinical doses of the virus thereafter. For this reason, the disease is rare among the adult native population.

In a series of 153 unselected cases treated in R.N. Hospital, 7 (4·6 per cent.) were Maltese. Two were recruits who had just joined the Royal Navy from the Maltese community in Corfu, and two of the men had been in sea-going ships during the previous summer. Their brief sojourn in hospital, shown in Table 3, indicates the mildness of the fever.

Table 3.

Maltese Ratings who suffered from Phlebotomus Fever in a series of 153 cases.

No.	Name	Rating	Age Years	Duration in Hospital Days	Remarks	Where Living in 1944
1.	J. Cauchi	O/Steward	23	5	Mild Case	H.M. Ship in Mediterranean.
2.	J. Azzopardi	Stoker	25	6	Mild Case	Corfu, Greece.
3.	A. Sicluna	L/Steward	34	6	Mild Case with gastro-enteritis	H.M. Ship in Mediterranean.
4.	J. Cauchi.	A.B.	20	8	Mild Case	Corfu, Greece.
5.	M. Spiteri	Stoker	23	5	Mild Case	Malta.
6.	J. Muscat	Stoker	18	7	Mild Case	Malta (Civilian)
7.	J. Stafrace	O/Steward	28	7	Mild Case	Malta.

These men were in naval barracks with easy access to medical advice. In the civilian population, the disease is very rarely seen by the Maltese general practitioners. The somewhat high proportion in the above series suggests that the fever may occur mildly in a number of Maltese each year, but the illness is so trivial that medical advice is not sought. Such an occurrence would allow the virus to maintain its virulence from year to year as the result of human passage. The data gives no indication that the immunity in Maltese naval ratings diminished during sea service.

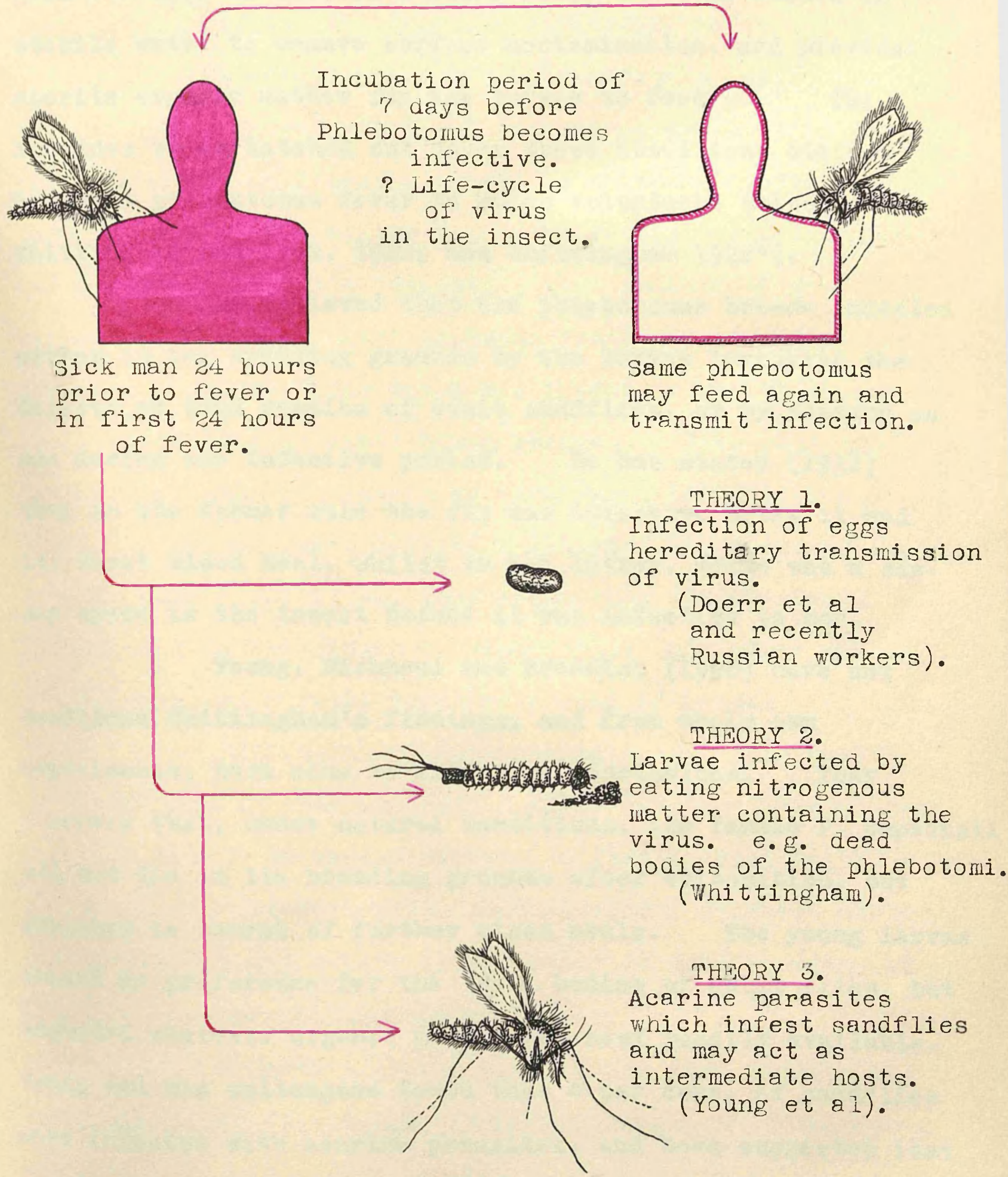
Doerr et al. (1909) found that after a feed of infective blood, Phlebotomus papatasii did not become infective for 7 to 10 days. This was confirmed by Birt (1910[2]) and Shortt, Poole and Stephens (1934[1]). From this evidence, it would appear that there is an interval of about a week between the ingestion of the virus and the insect becoming infective. Any changes in the virus taking place inside the insect during this interval are as yet unknown (fig. 3).

Another unsettled point, although considerable work has been done on it, is the question of how the virus survives the winter, when adult flies are absent. Doerr and his co-workers (1909) suggested that the virus was transmitted by the infected female sandfly through its ova from one generation to the next.

Whittingham (1924) claimed from his experiments in Malta and England that phlebotomi were infected in their breeding grounds and hereditary transmission was unlikely. He reared phlebotomi in cages with Maltese soil and organic matter in the form of dead insects or lizards faeces, and found that these flies were capable of transmitting sandfly fever, but in his experiments, only after they had received their first meal of blood. He, therefore, suggested that

Figure 3.

CYCLE OF INFECTION AND RESERVOIR OF VIRUS. (DIAGRAMATIC).



the virus survived the winter either free in the soil or within the bodies of the phlebotomus larvae.

He then bred flies in sterile breeding cages, from the eggs of infective flies which had been washed in sterile water to remove surface contamination, and provided sterile organic matter for the larvae to feed on. The imagines which hatched out under these conditions did not transmit phlebotomus fever to human volunteers (also, Whittingham and Rook, 1922, and Whittingham 1922[2]).

He believed that the phlebotomus became infected either in the breeding grounds by the larvae ingesting the dejecta or dead remains of adult sandflies, or by feeding on man during the infective period. He has stated (1938) that in the former case the fly was infective after it had its first blood meal, whilst in the latter, there was a six-day cycle in the insect before it was infective to man.

Young, Richmond and Brendish (1926) have not confirmed Whittingham's findings, and from their own experiments, have come to different conclusions. They observed that, under natural conditions, the female P. papatasii did not die in its breeding grounds after oviposition, but returned in search of further blood meals. The young larvae showed no preference for the dead bodies of adult flies, but ingested whatever organic matter was most readily available. Young and his colleagues found that 4 per cent. of sandflies were infested with acarine parasites, and have suggested that these mites could conceivably act as intermediate carriers of the virus. However, Young agreed with Whittingham on the most important point - that before an outbreak of sandfly fever occurred, an infection of the insect in the breeding grounds must be postulated.

Whittingham (1924) proved that all phlebotomi were not infected with the virus of sandfly fever.

Moshkovsky and his collaborators (1936) starting with ova from large numbers of phlebotomi which had fed on patients with the disease, proved in a series of experiments that certain of the adults reared from these ova, away from any contact with their 'parents', were capable of producing typical phlebotomus fever in human volunteers. That the disease was phlebotomus fever was proved by serial passage of the infection to other human beings. This work supports Doerr's original suggestion of hereditary transmission of the virus. In any case, infection followed the bites of recently hatched female sandflies, thus disproving Whittingham's assertion that the virus was transmitted only after the phlebotomus had already digested a meal of blood.

Manson-Bahr (1945) remarked that this was the only instance in which an animal virus had been transmitted hereditarily by an insect vector. This finding might be an important epidemiological consideration; it would explain the suddenness and extent of outbreaks of sandfly fever at the beginning of the hot weather.

Dolmatova (1942) studied the life history of P. papatasii at Stalinabad (in Middle Asia). He accepted the view of hereditary transmission of the virus, and claimed that the P. papatasii was an efficient vector of sandfly fever owing to this transmission of the virus to the ovum.

The weight of evidence is in favour of the Russian view of hereditary transmission of the virus. However, two points are clear:-

(1) Infection of the phlebotomus takes place in the breeding grounds. Therefore, any conditions which favour the survival of larger numbers of phlebotomi will lead to larger numbers of potentially infected vectors, and tend to cause an epidemic, if sufficient susceptible human beings are in the area.

(2) The virus survives the winter in the breeding grounds, probably by one or more of the methods described above (Fig. 3).

Clinical Picture.

General.

During the author's investigation, it was not possible to carry out a detailed clinical survey on a large series of cases. The personal observations in the following pages are based on this experience, and notes kept on 153 cases followed from admission to hospital until discharge.

A brief outline of the clinical picture will be given, followed by a more detailed consideration.

After an incubation period of about three to seven days, and a short prodromal stage of malaise and anorexia, the onset of the fever is sudden. There is usually chilliness, often with some shivering; rigors at this stage have been reported. The most constant symptom is severe frontal headache, with pain at the back of the eyes, accentuated by pressure on the globes or movement of the eyes. Frequently there is giddiness and photophobia. There are 'influenzal' pains in the back and legs, and asthenia. The patient becomes drowsy, apathetic and irritable if roused, but suffers from insomnia. At this stage, about the end of the first 24 hours of the fever, the sufferer is prostrate and ill. The face is flushed and may look swollen; the conjunctivae are injected. There is no lachrymation or respiratory catarrh. Anorexia with slight epigastric pain is common and constipation the rule, though diarrhoea and vomiting are seen occasionally. The centre of the tongue is coated with a white fur, and there is slight congestion of the fauces. The skin may be dry and

and hot, or drenched with perspiration. The temperature remains elevated for about twenty-four hours, then begins to fall gradually over the next few days, and is usually normal by the fourth day of the disease. The pulse rate is relatively slow. The blood picture usually shows a leucopenia with an absolute decrease in the number of polymorphonuclear leucocytes.

The patient usually gets better rapidly, though convalescence may be protracted by mental depression, lethargy and insomnia.

Incubation Period.

The usual incubation period is three to seven days. The following table gives the length of the incubation period as given by various observers:-

Table 4

Incubation Period.

Observers	Incubation Period Days	Remarks
Birt (1915)	4 - 7	---
Graham (1915)	2 - 4	---
Jewell and Kauntze (1932)	3 - 9	Infection from sandflies.
Shortt, Poole and Stephens (1934[1])	3 - 10	Infection from sandflies. (3 - 4 days in inoculation experiments).
Whittingham (1938)	5 - 7	---
Anderson (1941)	6 - 10	Inoculation experiments.
Sabin et al. (1944[1])	2½ - 6	Inoculation experiments.
Manson - Bahr (1945)	4 - 7	---

On several occasions during the 1945 epidemic in Malta, sailors whose ships had arrived in the harbour three days previously were seen in the early stages of the fever. In these cases, the almost invariable story was that the patient had been granted over-night shore leave on the night of arrival, and had slept the night in one of the sandfly infested lodging-houses in Valetta.

Onset.

The onset is usually sudden.

Birt (1910[2]) found that a history of a few days malaise made it difficult to determine the beginning of the pyrexia. Chilliness, nausea, headache, heaviness and discomfort about the eyes, lumbar pain and stiffness of the muscles of the lower extremities and somnolence induced his cases to take to their beds early. They found themselves unfit for duty next morning and reported sick, usually with temperatures of about 102° F. and a pulse rate of 70 to 80 per minute.

Anderson (1941) has stated that in about 50 per cent. of the cases observed by him, there was a short rather vague premonitory period, during which the patient felt slightly 'off-colour', with lassitude, loss of appetite, and slight muscular discomfort.

Similar prodromata have been observed by many others. In my experience, a history of slight malaise and mental dullness for about 24 hours before the onset of the fever and acute symptoms was fairly common. Cases often reported chilliness as an initial symptom, but in no case was a rigor observed. In a number of patients in hospital who developed the fever, the commonest findings during the onset were drowsiness, giddiness and anorexia.

Symptomatology.

Once the temperature has risen, the symptomatology, especially during an epidemic, is fairly clear. It is well summarised by Anderson (1941) in the following table compiled from his series of 78 proved cases of phlebotomus fever:-

Table 5.

Signs and Symptoms of Phlebotomus Fever, (Anderson 1941).

Symptoms.	Percentage Occurrence in Severe Cases	Mild Cases.
Headache.	100	100
Malaise.	100	100
Pain behind Eyes.	96	77
Photophobia.	70	28
Backache.	92	55
Myalgia.	92	63
Physical Signs.		
Hot dry skins.	100	100
Flushing of face.	100	81
Conjunctival Suffusion.	100	100
Pain on moving eyes.	80	33
Coated tongue with clean red margin.	94	64
Faucial injection.	73	80
Bradycardia.	100	100

(a) Fever.

Pyrexia is a most constant sign of the disease, and is usually present even in very mild cases.

Sabin and his colleagues (1944[2]) found that in more than 100 cases of experimentally produced phlebotomus fever 65 per cent. had temperatures of 102° F. or more. The highest temperatures recorded were in the region of 104·5° F., and only 2 per cent. had temperatures under 100° F. In this series, the duration of the fever varied from one day to as long as nine days. The two, three and four day fevers constituted 85 per cent. of the total.

Walker and Dods (1941) in their studies of an outbreak in 1940 among the Australian Imperial Force stationed in Southern Palestine, found that in the cases of naturally occurring phlebotomus fever, 2 per cent. had a temperature of 104° F, in 6 per cent. the temperature reached 103° F., and on the average, the greatest temperature was in the region of 102·5° F. They also found that the duration of the pyrexia was more than three days in many cases.

In a random series of 153 cases in the 1945 epidemic in Malta, the maximum temperatures are shown in Table 6, and the duration of the fever in Table 7.

Table 6.

MAXIMUM TEMPERATURES
In Series of 153 Cases in Malta, 1945.

Temperature in degrees. F.	Number of Cases	Percentage of Total
99 and less	4	2·6
99 - 100	13	8·5
100 - 101	29	19·0
101 - 102	33	21·6
102 - 103	37	24·3
103 - 104	30	19·5
104 - 105	7	4·6
Total	153	

Table 7.

DURATION OF FEVER
In Series of 153 Cases in Malta, 1945.

Number of days.	Number of Cases	Percentage of Total
1	10	6·5
2	51	33·3
3	59	38·5
4	20	13·0
5	10	6·5
6	2	1·3
7	1	0·7
Total	153	

After admission to hospital, 64·9 per cent. of cases had maximum temperatures ranging between 100° F. and 103°F., whilst 24·1 per cent. had temperatures above 103° F., 11·1 per cent. had temperatures of 100° F., or less. Of the last group, a number of these cases were seen late in the disease, and the temperature was probably higher prior to admission.

As to the duration of the pyrexia, 84·8 per cent. had two, three or four day fevers, a similar figure to that obtained by Sabin et al. (1944[2]) in their series of experimentally produced cases.

Table 8 gives a comparison with the figures of the earlier workers.

Table 8.

Comparison of Duration of Fever in Several Epidemics.

Place and Worker.	Number of Cases	Duration of Pyrexia in days per cent.					
		2 and less	3	4	5	6	7 and more
Malta (Birt 1915)	243	20	30	23	12	9	5
Nashera (Birt 1915)	160	-	22	27	24	20	6
Lemnos Lambert 1918)	237	1	14	29	31	12	9
N. Africa (Sabin et al. 1944[2])	100	28	43	20	4	2	3 X
Malta, 1945. Author's nvestigations)	153	40	38.5	13	6.5	1	1

X Experimentally induced phlebotomus fever.

It shows that the febrile period was less in the author's investigation. This may have been due to the admission to hospital of a number of cases late in the disease, but judging from the clinical descriptions it is my view that the fever in Malta in 1945 was a milder variety than that seen before and during the First World War.

The type of temperature curve most usually recorded shows that the peak is reached on the first or second days, and is followed by gradual defervescence. Typical charts are shown in figures 4 and 5.

From the above investigations it can be concluded that in phlebotomus fever elevation of temperature is a constant finding; it varies with the severity, and is usually highest on the first or second days of the disease. They also confirm the observation first made by Lambert (1918) that the name 'three-day fever' as applied to the disease is misleading, since the pyrexial period may vary from two to eight days, or more.

Occasionally, the temperature rises again after it has been normal for a day or two (McArthur 1942, Sabin et al. 1944[2], Anderson 1941) but the rise is usually slight and much less marked than that of dengue.

(b) <u>Pulse Rate.</u>

Bradycardia in phlebotomus fever is almost always present. On the first day of the disease, the pulse rate is usually elevated, sometimes in proportion to the fever (Sabin et al. 1944[2], Walker and Dods 1941, and personal observations.) But very soon the pulse becomes slow in

Figure 4.

Typical Temperature Charts.

DISEASE.
SAND -FLY FEVER.

Notes of Case.

Name DUFFY, William.

Age 40 years.

Diet

Case Book No

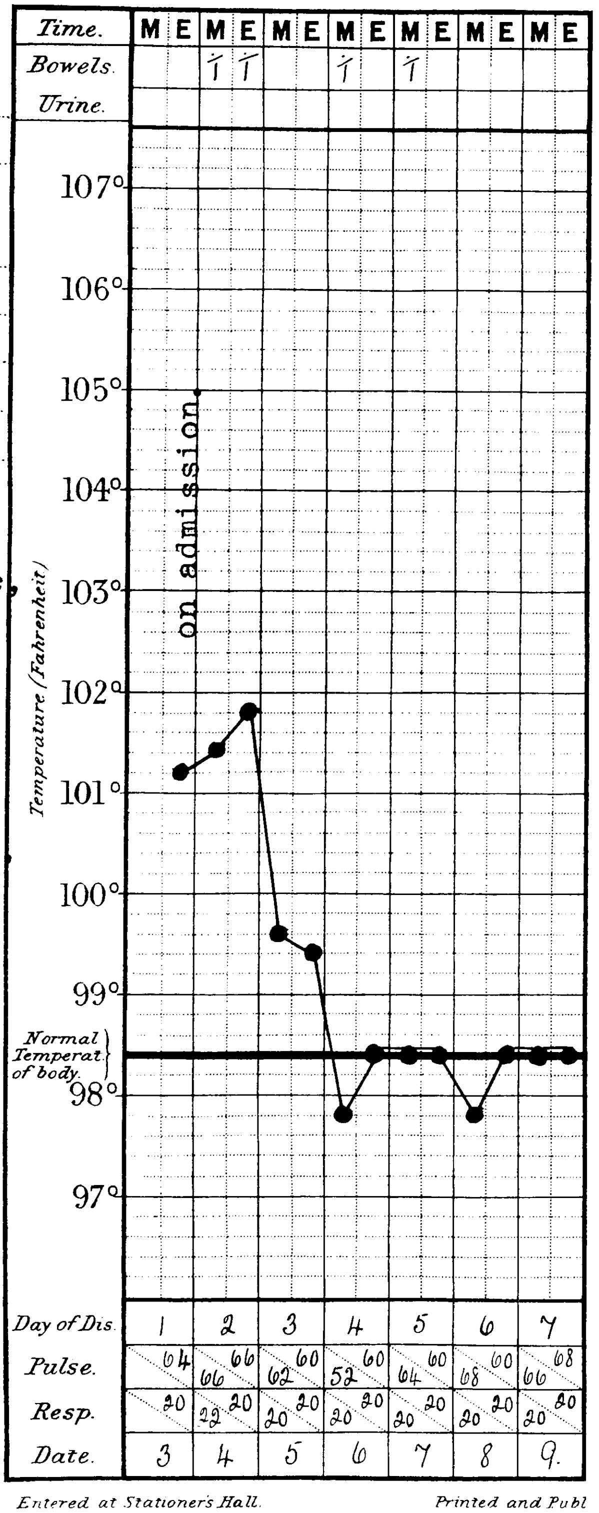
On admission complaining of.-
Frontal headache,
Giddiness,
Weakness,
Aches in limbs and small of back.

On examination.-
Mental confusion,
Conjunctivae suffused,
Slight nuchal rigidity,
Photophobia,
Tender eyeballs,
Pain on eye movements.

One month in Mediterranean.

Date of admission.
3rd June, 1945.

DISCHARGED. ~~Result.~~ 12th June, 1945.



DISEASE.
SAND-FLY FEVER.

Notes of Case.

Name WRIGHT, Harry A.

Age 28 years.

Diet

Case Book No

On admission complaining of.-
Frontal headache
Pain in eyes,
Malaise,
Shivering and sweating.

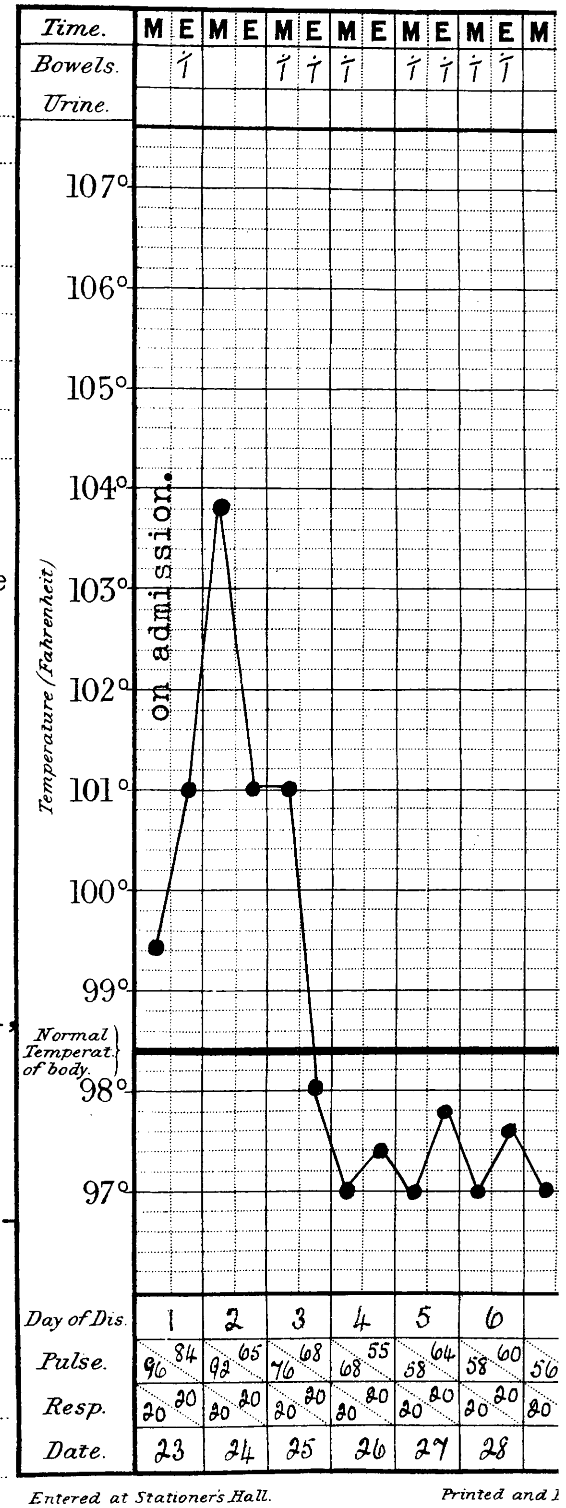
On examination.-
Eyes suffused,
Sweating,
Tongue coated with white fur clean at tip and edges,
Fauces congested,
Eyeballs tender.

24th June symptoms worse with some mental confusion thereafter condit- -ion gradually improved.

FOUR MONTHS IN MEDITERRANEAN.

Date of admission.
23rd June, 1945.

DISCHARGED. ~~Result.~~ 29th June, 1945.



DISEASE.
SAND-FLY FEVER.

Notes of Case.

Name WARD, Frederick.

Age 19 years.

Diet

Case Book No

On admission complaining of.-
Frontal headache,
Aches all over,
Dry throat,
Headache on previous day, could not sleep owing to fever- -ishness and pains behind the eyes.

On examination.-
Flushed, hot dry skin,
Many insect bites
Conjunctivae suffused,
Photophobia,
Pain on moving eyes.
Tender eyeballs.

Five months in Mediterranean.

Date of admission.
14th June, 1945.

DISCHARGED. ~~Result.~~ 20th June, 1945.

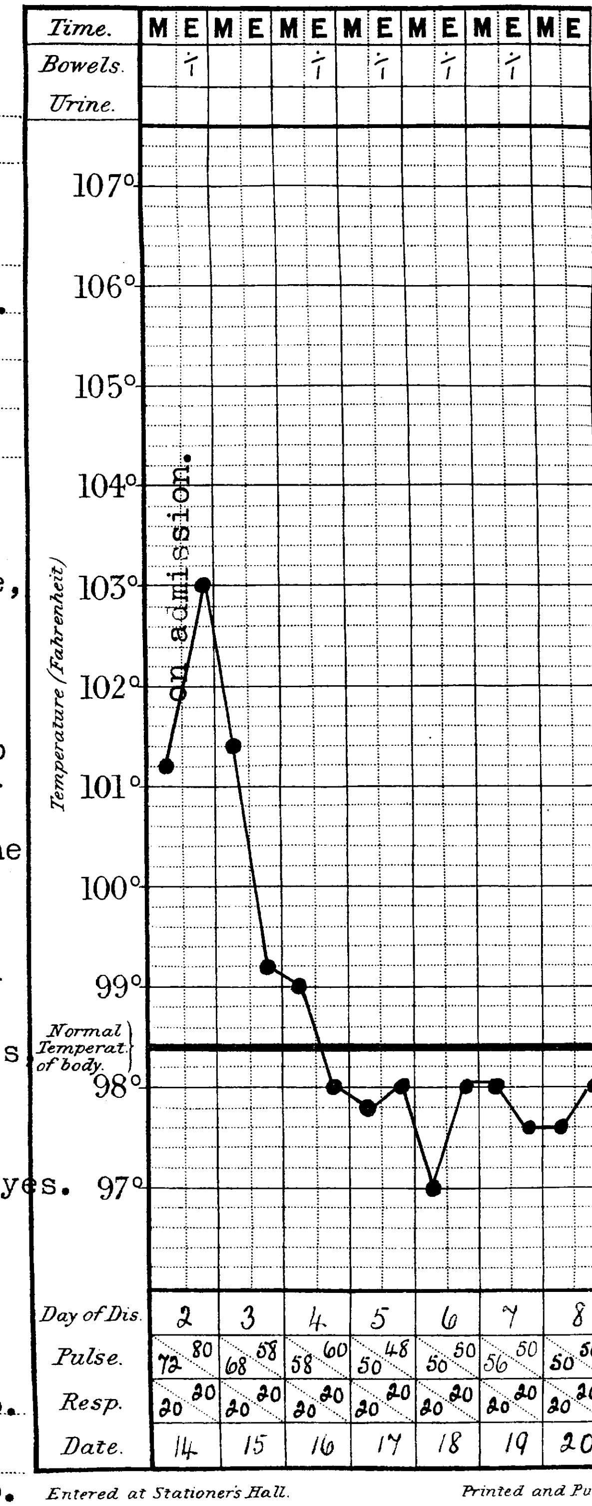


Figure 5.

Typical Temperature Chart.

DISEASE.

SAND-FLY FEVER.

Notes of Case.

Name BROWN, Arthur,

Age 20 years.

Diet

Case Book No.

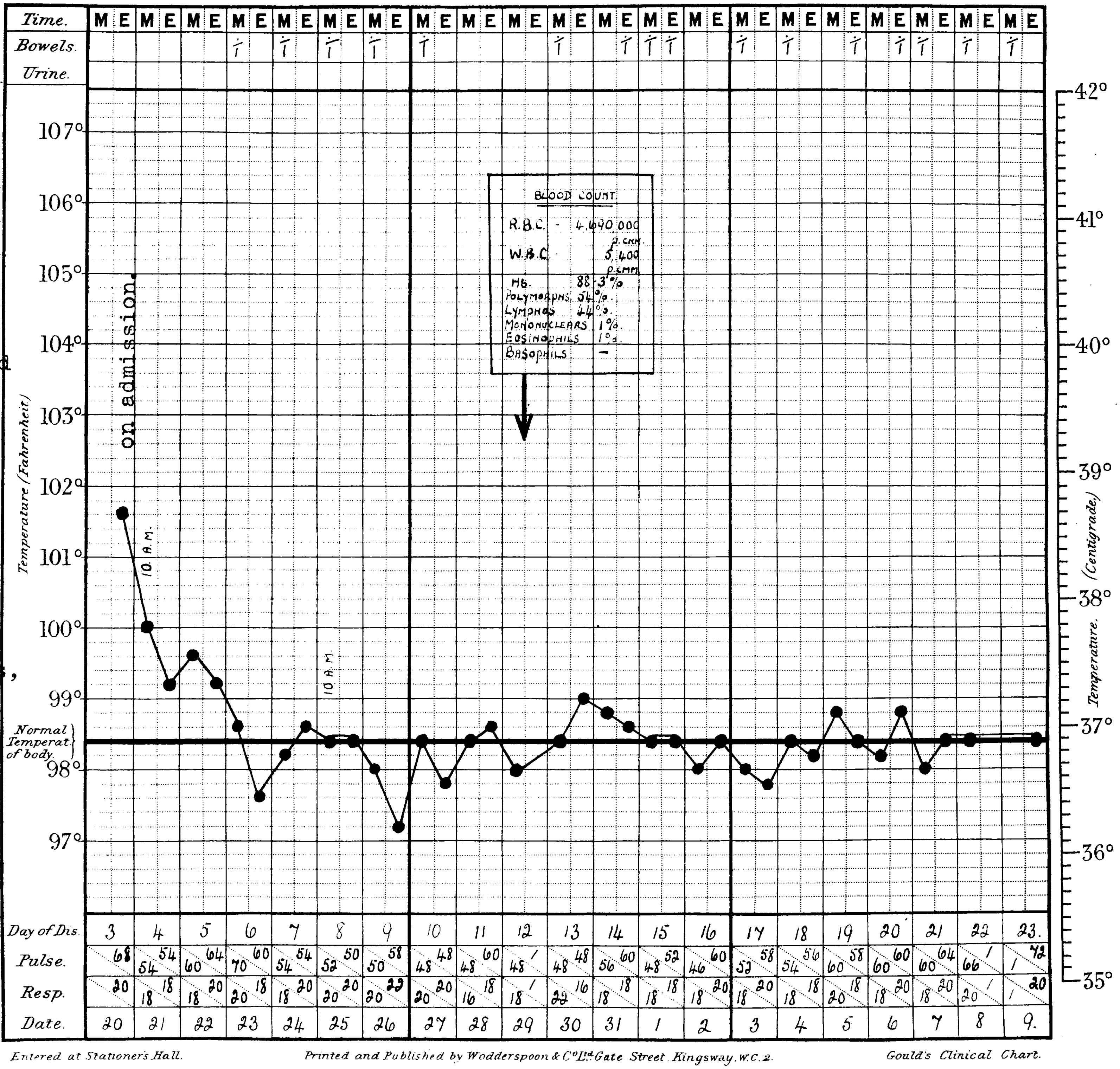
Two days prior to admission developed frontal headache and drowsiness, felt feverish but did not report sick. Gradually got worse.

On admission complaining of. -
- Frontal headache
- Drowsiness,
- Giddiness,
- Generalised aches,
- Weakness.

On examination. -
- Conjunctivae suffused,
- Pain on moving eyeballs,
- Profuse sweating,
- Numerous insect bites on skin.

Date of admission. 20th July, 1945.

~~Result~~ DISCHARGED. 12th August 1945.



relation to the pyrexia; during convalescence an absolute bradycardia is common. Typical pulse temperature data is given in figures 4 and 5. Walker and Dods (1941) found in their cases that by the time the temperature was normal, the average pulse rate was 60 per minute, and that a rate of 50 or even less was often found lasting several days into convalescence.

Sabin et al. (1944[2]) stated that a true bradycardia was not always present, but when it occurred, usually at the end of the febrile period, or during convalescence, the pulse rate was in the range of 40 to 60 per minute. They found that the blood pressure was frequently low during the disease and convalescence.

Shortt et al. (1934[1]) and Anderson (1941) have stressed the value of bradycardia as a point of importance in the differential diagnosis of sandfly fever from other causes of pyrexia. In Malta, I found the presence of bradycardia a most useful sign.

(c) Nervous System.

Apathy and drowsiness occur during the febrile period; insomnia is frequent and may persist for several nights.

Headache, usually severe, and characteristically frontal or behind the eyes is almost invariably present.

Anderson (1941) has stated that the typical 'sandfly headache' appeared to be 'low frontal', extending into the orbits'.

In severe cases the headache may involve the occipital area, or appear to be generalised. Giddiness is often present, and accompanies the headache.

Walker and Dods (1941) described areas of hyperaesthesia of the skin over the lower part of the neck and upper part of the abdomen.

The pupillary reflexes are normal and the knee jerks and abdominal reflexes unaltered, although they may tend to be sluggish. There is no true nuchal rigidity, but the neck may be painful due to myalgia.

(d) Eyes.

Conjunctival suffusion is present in almost every case, and the intensity of the congestion depends on the severity of the attack. Photophobia is common, and may be intense, causing the patient to hold his hand over his eyes. There is pain on movement of the eyes, which Anderson (1941) has suggested is due to myalgia of the orbital muscles. The eyeballs are almost always tender on pressure.

Shee (1942) has described varying degrees of choking of the optic discs in twenty-seven out of thirty cases of sandfly fever. The condition ranged from blurring of the edges of the discs with distension of the retinal veins to frank papilloedema. It was seen in the earlier stages of the fever, but was sometimes more marked on the second day. In severe cases it was still visible on the day after the temperature had started to fall. It has been regarded as being due to an increase in the pressure of the cerebrospinal fluid. This sign should prove of value in the diagnosis of doubtful cases if Shee's findings are confirmed by further investigation.

(e) The Mouth and Throat.

A number of workers (Birt 1910[2], Whittingham and Rook 1923[1] and others) have stated that the tongue is coated with a whitish yellow, or whitish brown, fur, on the dorsum, whilst the margin and tip remain red and clean. In my experience this appearance of the tongue was a frequent finding. But in other febrile diseases, especially infective hepatitis, the tongue had a similar appearance. Therefore, whilst the sign is worth noting, it was not of much diagnostic value.

Some clinical observers (Whittingham 1938, Anderson 1941) have described faucial congestion as common in sandfly fever. Sabin and his co-workers (1944[2]) have stated, "In the mouth one may find congestion of the fauces, soft palate and posterior pharyngeal wall, but the pronounced swelling or redness of the tissue seen in bacterial infections of the throat was not encountered." My observations were similar to those of Sabin, but in the hot, dusty summer weather of Malta, slight degrees of faucial congestion were not uncommon in healthy persons.

Birt (1910[2]) Whittingham (1938) and Walker and Dods (1941) have described the presence of crops of vesicles without inflammatory reaction at the junction of the hard and soft palates. Sabin et al. (1944[2]) failed to observe these vesicles in their cases of experimentally produced phlebotomus fever. Walker and Dods (1941) suggested that the presence of these vesicles was a feature of a number of virus infections as contrasted with other infections. They had observed similar vesicles in cases of infective hepatitis.

I found the vesicles as described in a number of cases of phlebotomus fever in 1945, but they were also observed in patients suffering from infective hepatitis and other diseases. In addition, the vesicles were found without giving rise to any symptoms in the throats of a number of apparently healthy individuals.

At present, the evidence on the significance of these vesicles is inconclusive.

(f) <u>The Skin.</u>

The skin may be hot and dry or covered in perspiration. Usually it is hot and dry in the early stages, and the sweating is most marked with the falling temperature. A characteristic finding in this disease is flushing of the face. The erythema usually covers the face, neck and occasionally the upper part of the chest. The face has also a somewhat swollen appearance, and is usually shining with sweat. This appearance of the face, with the blood-shot eyes, gives rise to the typical 'sandfly facies'. The flushing of the face and neck closely resembles sunburn and in sailors appears on the area commonly exposed by their uniforms. On several occasions the intensity of the erythema was an aid to diagnosis as the patients were known to me beforehand and the change in their appearance could be appreciated.

True skin rashes are rare, but do occur. They are usually blotchy erythematous or maculo popular patches. In 1945, I examined only one sandfly fever patient who had an erythematous rash on his face, trunk, arms and thighs; within a few hours the rash became pale and macular except on the face, where it remained erythematous. Within 24 hours it had completely faded, and left no staining. Whilst the rash at first suggested rubella, the marked conjunctival injection, frontal headache and other clinical evidence was in favour of a diagnosis of phlebotomus fever. In cases of this disease large numbers of insect bites are frequently seen on the exposed parts of the body.

(g) Muscles.

Pains in the muscles of the back, especially in the lumbar region, and in those of the arms and legs, are common. The backache may be severe.

Anderson (1941) stated that in his series, the muscles were sometimes tender to palpation. Also, that the pain on moving the eyes was due to myalgia affecting the eye muscles. He found that most of the joint pains complained of by patients turned out to be pain in the muscles round the joint. Only one patient in his series had a true arthralgia, which was referred to the knees.

(h) Gastro-Intestinal System.

Anorexia is a constant feature. Nausea and vomiting are rare. Constipation is common during the febrile period, but diarrhoea is sometimes present.

During the 1945 outbreak, especially at the beginning, a number of cases of sandfly fever in which diarrhoea was a prominent symptom were admitted to hospital. As many of these patients were new-comers to Malta and had probably contracted phlebotomus fever during all night shore leave, it was thought probable that they were suffering, in addition, from a type of gastro-enteritis common in Malta ('Malta Dog') as a result of the contaminated food they had eaten in the local restaurants.

(i) General.

In phlebotomus fever there is no enlargement of the lymphatic glands as there is in dengue: nor do the spleen and liver become palpable.

Franz, in the paper by Doerr, Franz and Taussig (1909) stated that epistaxis sometimes occurred and, with diarrhoea, were common after the second day. Epistaxis has been reported by others (Whittingham 1938, Lambert 1918, and others), but none of the cases observed by me during 1945 had epistaxis.

Doerr and Russ (1909) claimed that the first cases in an outbreak were usually mild. They suggested that the virulence of the virus appeared to be diminished in the passage from the adult fly to its offspring, and was regained after passing through man again. In 1945, a considerable number of severe cases were seen during the first weeks of the epidemic, and no evidence to support the above view was obtained.

There are no complications.

Clinical Types.

Anderson (1941) suggested that a clinical classification of cases of phlebotomus fever into two types, severe and mild, was advantageous. In the severe type, the clinical syndrone was definite, and there was no doubt about the diagnosis. But in the mild type, the clinical picture was less definite and some features traditionally associated with the disease were absent. He emphasised that this was a clinical classification, and there was no clear line of demarcation between the two types. The disease varied from very mild febrile upset in some individuals to a severe debilitating fever in others.

Pathology.

As sandfly fever is probably never fatal, little is known about the tissue changes during the acute stage of the infection.

Anderson (1941), on the clinical evidence, tentatively suggested that the tissues most affected by the virus were those of ectodermal and, to a lesser extent, of mesodermal origin, whilst tissues developed from the entodermal layer appeared to be only slightly affected.

Clinical Laboratory Investigations.

(a) Urine.

The urine is often dark coloured and scanty, due to loss of fluid by sweating, but otherwise normal in its constituents.

(b) Cerebrospinal Fluid.

Le Gac and Albrand (1937) examined the cerebrospinal fluid in 14 cases of the disease, and found that there was an increase in the pressure, albumin, cell content (10 - 110 lymphocytes per C.mm.); and a slight decrease in chlorides. The colour of the fluid and its sugar content were normal, and in cultures, no bacteria were found.

Whittingham (1938) stated that the cell content was slightly increased (about 11 leucocytes per C.mm) the cells being chiefly lymphocytes, and the protein content was somewhat raised, but did not exceed 50 mgm. per 100 c.c.

On the other hand, Sabin and his co-workers (1944[2]) performed 5 lumbar punctures on volunteers suffering from experimentally produced phlebotomus fever: two on the first day and three on the second day of the disease. The cerebrospinal fluid was not under pressure, and was normal as regards cells, protein, sugar, chlorides and the colloidal gold test. Inoculation of the C.S.F. in large doses into human beings did not produce the disease, whilst the blood serum from the same volunteers did.

(c) Blood.

Whittingham (1922) reviewing the literature, showed that Dr. Skey, as early as 1816, had remarked on the absence of the 'buffy-coat' in specimens of blood in the short summer fever of the Mediterranean.

McCarrison (1906) in his cases in the Chitral, reported the presence of leucopenia, with a relative decrease in the number of polymorphs, and an increase in the large mononuclear leucocytes. This increase has not been confirmed by subsequent workers.

The leucopenia associated with this disease was also noted by Doerr and his co-workers (1909) and Birt (1910[2]).

The latter stated that in a differential white cells count, the polymorphs were usually in the region of 57 per cent. instead of 65 to 70 per cent.

Whittingham (1922) from his investigations, concluded that at the onset of the fever there was a slight leucocytosis, which passed off in a few hours. This was followed by a leucopenia which lasted three to four days, and that on the fourth day of the disease the total white cell count might fall to 3,500 per c.mm. On about the tenth day of the disease he observed a transient leucocytosis in several cases.

Kennedy (1937) showed that in the course of the fever many immature polymorphs appeared in the blood picture, with a shift of the Arneth index to the left. He found the leucopenia most marked on the first and second days and an absolute decrease in the number of polymorphonuclear leucocytes, with a relative lymphocytosis. A striking character of the white cells was the large proportion which showed degenerative changes. Also, these alterations in the blood picture could persist in varying degrees for three to four weeks after the fever. He found the eosinophils reduced during the fever, but they returned to normal early in convalescence.

Kennedy summed up his findings thus, "Although the fever is short and never fatal, the disease is characterised by an aftermath of depression, both mental and physical, which may last for months. This is more understandable when it is seen what a profound alteration in the blood picture results from an attack."

Sabin et al. (1944[2]) carried out a large number of total and Schilling leucocyte counts in over 150 cases, and reached the following conclusions:-

1. The disease may or may not be associated with a true leucopenia, but a pronounced relative and absolute reduction in the number of segmented neutrophils associated with a simultaneous definite relative and absolute increase in immature neutrophils (chiefly the staff cells) is a constant feature.

2. A reduction in the total number of leucocytes to below 5,000 per c.mm. from a higher normal level may be expected in approximately 90 per cent. of cases during the course of the disease.

3. The leucopenia is rarely encountered on the first day of the fever, but is most marked in the first two days of the post febrile period.

4. During the second or third days of the fever, the number of lymphocytes may constitute 40 to 65 per cent. of the total white cells. At the same time, the number of segmented neutrophils begins to drop and immature cells increase to a point at which they usually outnumber the segmented cells.

5. The mononuclear leucocytes are usually normal throughout, but in some patients a definite increase occurs. The eosinophils occasionally disappear during the course of the disease, and there is no eosinophilia during convalescence. The normal blood picture usually returns five to eight days after defervescence.

They considered that the changing relationships between the different types of leucocytes at various stages of the disease were of the greatest importance in aiding diagnosis. Like Kennedy, Sabin and his colleagues have stressed the low polynuclear index which is found in phlebotomus fever.

Sabin and his co-workers (1944[2]) also found the erythrocyte sedimentation rate, serum phosphatase estimations, and the Hanger cephalin - cholesterol flocculation test for hepatic damage showed no significant alterations in phlebotomus fever.

Serological and other tests.

Numerous unsuccessful attempts have been made to find a diagnostic test for this disease.

Anderson (1941) made cultures of the virus in chick embryos, using samples of blood from 132 patients clinically diagnosed as phlebotomus fever. Positive cultures were obtained in 78; doubtful in 14, and negative in 40. Obviously little importance can be attached to negative results.

Sabin et al. (1944[2]) tried unsuccessfully, using acute and convalescent sera, to devise:-

(a) A precipitin reaction.

(b) A complement fixation reaction.

(c) A skin test.

(d) An agglutination or haemolysis reaction, using sheep and chicken red blood cells.

(e) A test for the presence of cold agglutinins.

Differential Diagnosis.

The diagnosis of phlebotomus fever has to be made on clinical and epidemiological grounds. The disease occurs during the summer and autumn months in endemic areas, the time of year when other infections are active in warm countries. The appearance in a number of individuals of a clinical syndrome consisting of a short sharp fever, accompanied by frontal headache, slow pulse, injected conjunctivae, muscular pains, together with leucopenia with neutropenia and an increase in the number of immature neutrophils, may reasonably warrant a diagnosis of an outbreak of phlebotomus fever.

The main diseases liable to be confused with phlebotomus fever are dengue, influenza, malaria and, in their early stages, the enteric group of fevers, undulant fever, relapsing fever and typhus.

Dengue fever is more closely related to phlebotomus fever than any other disease and resembles it closely. Injected eyes, muscular pains, bradycardia and leucopenia occur in both diseases. The main features of dengue which help to distinguish it are, the pyrexia is usually longer, and there is the typical saddle-back temperature curve. Lymphadenopathy is common in dengue, but absent in phlebotomus fever. Skin rashes, scarlatiniform on the first day and macular on the fifth are common in dengue.

In 1945, there was no dengue in Malta. The vector (Aedes aegypti) is prevalent on the island, and outbreaks of dengue fever have been recorded in the past.

Recently, Karamchandani (1946) has called attention to the common features of dengue, phlebotomus fever and certain other short term fevers common in tropical countries. He suggested that these were varieties of same disease produced by differences in the strains of the virus or in the susceptibility of the patient. Until experimental evidence is produced to support this view, I consider it should be treated with reserve.

Influenza epidemics rarely occur in the summer, and coryza and bronchitis are not seen in phlebotomus fever.

The diagnosis of malaria depends on the finding of the specific parasites in a blood film. If the patient has been taking mepacrine recently, the parasites are often absent. Rigors, at the onset, are common in malaria and rare in phlebotomus fever. A leucocyte and differential count may help to establish the diagnosis. In mild or atypical cases accurate differentiation may be impossible.

The enteric group of fevers are at times atypical, especially in patients who have been inoculated with the protective vaccine. The febrile period may be short and, in addition, bradycardia and leucopenia occur in the enteric fevers. However, closer examination of blood films for the presence of immature neutrophils and agglutination tests will usually reveal the true nature of the infection.

Undulant fever as a cause of pyrexia and general malaise in the summer months may lead to difficulty as neutropenia is often present. But this infection is of longer duration, profuse sweating is common, and the patient has a history of feeling well in the morning and ill later in the day, usually for some weeks previously. Agglutination tests for Brucella will confirm the findings.

Relapsing fever, when it occurs in sandfly areas, may, at its onset be mistaken for phlebotomus fever, but the leucocytosis, and the finding of the spirochete in blood smears will give the diagnosis.

The onset of typhus, with fever, severe headache, muscle pains and bloodshot eyes, may resemble phlebotomus fever, but in typhus there is tachycardia and leucocytosis. As the fever continues, the severity of the disease will become apparent and the onset of delirium will be noted. On the fifth day the typical macular rash appears. A positive Weil-Felix reaction confirms the clinical diagnosis.

The onset of Weil's disease may closely simulate sandfly fever, with headache, pyrexia, pains in the calves, conjunctival injection and prostration. But after four or five days, the appearance of jaundice, enlargement and tenderness of the liver, mucous and cutaneous haemorrhages, together with a polymorphonuclear leucocytosis which persists throughout will give the diagnosis. This can be confirmed by agglutination tests, which are positive after the first week. The L. icterohaemorrhagiae may be isolated by (1) culture from the blood or (2) by inoculation of the blood into a guinea pig.

Infective hepatitis in the pre-icteric stage may be a source of difficulty as neutropenia occurs in both diseases, and in mild cases exact differentiation may not be possible. The appearance of jaundice excludes sandfly fever.

In the outbreak in Malta in 1944, two cases of cerebrospinal fever were admitted to the R.N. Hospital, diagnosed phlebotomus fever. Bradycardia occurs in both diseases, and in cases of doubt examination of the cerebrospinal fluid will usually settle the diagnosis (Murray 1945).

During the summer of 1945, a patient, suffering from frontal headache, pains in the back, conjunctival suffusion, drowsiness and fever, was admitted to the hospital diagnosed as sandfly fever. Persistent tachycardia made this diagnosis doubtful. On further questioning, the patient complained of a slight pain in his left groin, and a small tender lymph gland could be felt. Gland puncture was performed, and a small gram negative organism found in the fluid obtained, which, on culture and further examination, proved to be Pasturella pestis. This was an early case of bubonic plague.

The diagnosis of phlebotomus fever, especially in sporadic cases, may be by no means easy. On the other hand, in the presence of an outbreak, there is a tendency to label all cases of pyrexia with indefinite signs, sandfly fever. Bulmer (1943) stated that in 18 months at a base hospital in the Middle East, there were 1,153 examples of short-term fevers in which a precise diagnosis was not established. 805 of these were considered to be sandfly fever, but in the absence of an epidemic, it was difficult to be certain of sporadic cases.

Convalescence.

Lassitude and mental and physical incapacity are common during convalescence. The patient, after an attack of sandfly fever, looks debilitated and 'washed out'. Mental depression occurs in a number of cases, and may take weeks to clear up. Return to duty too soon in my experience retarded complete recovery.

Table 9.

NUMBER OF DAYS IN HOSPITAL
In Series of 153 Cases.

Number of days	Number of cases	Percentage of Total
3 - 6	84	54·9
7 - 9	61	39·9
10 - 12	4	2·6
13 and more.	4	2·6
Total	153	

Table 9 shows the number of days in hospital in the series of 153 cases. Owing to the shortage of hospital accommodation, cases were discharged as soon as their temperatures had been normal for two or three days. The majority of patients were sent from hospital for a week's convalescent leave to a rest camp.

Treatment.

There is no specific treatment. Good nursing, and tepid sponging during the febrile period greatly adds to the comfort of the patient and encourages sleep. In the Royal Naval Hospital, Malta, the patients were given a dose of a mild diaphoretic, such as A.P.C. or Dover's powder, on admission. In cases where the headache was severe, 30 minims of Liquor Opii Sedativus, or Tinctura Opii 10 minims were found useful for giving relief. Two cases in hospital suffering from surgical conditions for which they were receiving sulphathiazole contracted the disease. Also, a number of cases who had been given sulphonamides prior to admission to hospital were seen. These drugs did not appear to have any effect on the disease.

No observations were made of the action of penicillin on the disease, but it is unlikely that it would have any beneficial effect.

It is important that all cases of phlebotomus fever should be nursed in sandfly nets during the first 48 hours of their illness to prevent the infection of other sandflies which may bite the patient.

Convalescent serum has not been used therapeutically; the short duration of the fever in most cases and the absence of complications do not justify its preparation and administration. The neutralizing effect of convalescent serum on serum containing the virus has been known for a number of years (Doerr et al. 1909). Recently, Shortt and his co-workers (1938) have shown that convalescent serum can prevent the formation of the typical lesion on the chorio-allantoic membrane of the chick-embryo when mixed with the virus.

IMMUNITY

General.

Doerr et al. (1909) found that the serum of an individual who had suffered from phlebotomus fever two years previously possessed protective antibodies against the virus. They proved that if 1 c.c. of the immune serum was mixed with 0·5 c.c. of infective blood, the virus was neutralised and no illness developed when the mixture was injected into a susceptible human volunteer.

Lambert (1918) concluded from his observations that a solid immunity resulted from one attack in 90 per cent. of cases; the remaining 10 per cent. suffered from second attacks which were usually mild in character.

Cullinan and Whittaker (1943), in an outbreak which involved two hospitals in the Middle East, have stated that second attacks occurred in 15 per cent. of their cases, and occasionally there were three separate attacks during the three months epidemic period.

Shortt and his co-workers (1935[1] and 1936) proved that whilst an attack of phlebotomus fever conferred a certain degree of immunity, which might persist for a year after an attack, the state was incomplete and the individual might suffer from a modified attack of the disease in a subsequent year.

Shortt et al. (1940) used as a vaccine the virus grown by egg-culture. In inoculated volunteers immune bodies were subsequently demonstrated.

Sabin et al. (1944[1]) proved that persons recovering from an experimental attack of the disease were immune on reinoculation with infective serum for at least four months thereafter. The same workers (1944[2]) also showed that serum containing the virus which had been irradiated with ultraviolet light appeared to be capable of producing immunity without giving rise to the disease.

The present day view has been summed up by Whittingham (1938) thus:

> "About 75 per cent. of new-comers to sandfly regions fall victims to phlebotomus fever during their first summer. The virus inoculated by one infected phlebotomus is capable of inducing the fever in a susceptible individual, but bites of numerous infected phlebotomi fail to cause disease in some people who appear to be naturally immune to this disease. In a few cases the fever recurs four to seven weeks after the primary attack; this is probably not a relapse but due to reinfection of an individual with a low resistance to the infection. About 15 per cent. of Europeans dwelling in sandfly fever districts suffer from a second attack during their sojourn. Probably a high proportion of Europeans suffer from second and third attacks so slight that they are mistaken for a slight chill, an attack of headache, or the effects of over-exertion in the heat. Children as a rule suffer less than adults. Natives contract the disease in childhood and thereafter by frequent subminimal infections maintain a complete immunity."

Multiple Attacks. (Personal Observations).

Several workers (Lambert 1918, Cullinan and Whittaker, 1943, and others) had remarked that certain individuals suffered from three attacks in the same epidemic, but no statistics to support this view were available. Therefore, it was decided to investigate the liability to more than one attack in the 1945 epidemic.

All patients admitted to the medical establishments in Malta suffering from sandfly fever were given a questionnaire, which, with guidance from the ward staffs, was completed prior to discharge. They were asked to state if they had previously suffered from sandfly fever in 1945 or in previous years. At the end of the epidemic period, a series of 500 cases, as far as possible consisting of men who were still in Malta and could be interviewed, or whose medical records could be checked, was obtained. The men were interviewed either by myself or the Sanitary Inspector and their statements checked from the hospital or sick quarters records.

The following results were obtained.

Table 10.

Investigation of the Frequency of
Second and Third Attacks of Sandfly Fever.

	Number of cases	Percentage of total
Number of Cases of Sandfly Fever under review.	500	100
Number of Cases who had ONE attack in 1945.	457	91·4
Number of Cases who had TWO attacks in 1945.	39	7·8
Number of Cases who had THREE attacks in 1945.	4	0·8
Number of Cases in the Series who had an attack in a previous year.		
1944	53	--
1943	11	--
Previous to 1943	7	--

Of the four men who suffered from three attacks, one was admitted to hospital for all three, another had his third attack diagnosed by the medical officer of his establishment, but was not admitted to hospital as the illness was mild. The other two cases were admitted to hospital with what was considered to be a second attack, and stated that they had suffered from a mild attack in the period between the first and second admission to hospital. The two men were intelligent, and were definite on this point, and have been included as having three attacks although medical confirmation was lacking.

In this series no man who had suffered from phlebotomus fever previous to 1945 developed more than one attack, but a number of cases who had suffered from the disease in 1944, suffered from severe attacks in 1945.

It is concluded that an attack of phlebotomus fever leads to a fairly solid degree of immunity in the majority of individuals. A small number of persons for some reason do not develop this immunity, and may suffer from a second attack in the same epidemic. On rare occasions, a person may suffer from three attacks in the one season. Although generally, phlebotomus fever in a person who has suffered from the disease in a previous year is mild, some individuals are severely attacked by the disease in consecutive years.

PROPHYLAXIS.

Review of Existing Preventive Measures.

No scientific efforts were made at prevention of this disease until Marett (1915), having found the breeding grounds of the phlebotomus, advocated rubble clearance and improved hygienic conditions in barracks.

The first extensive study of the prevention of phlebotomus fever was that published by Whittingham and Rook (1923[1]). They stated two fundamental conditions which had been proved by their earlier researches:-

1. "It is definite that the infection takes place in the breeding grounds, and it follows that prophylactic measures against the fever must be directed against the fly especially in such places."

2. "A sound knowledge of the habits and habitats of the phlebotomus is the keystone of successful prophylaxis. The insect, like many other pests of mankind, depends on organic matter to complete its life-cycle; it is encouraged by filth, and as with flies in general, so its prevalence is an index of the degree of cleanliness of any area. Consequently, the removal of its breeding places will reduce automatically the prevalence of other insect pests."

Although the method of prophylaxis used in the present investigation - attacking the mature phlebotomus in human habitations by wall-spraying with DDT - may require modification of the above statements, the underlying principles remain. For successful eradication of sandfly fever in any area, the insects must be attacked in their breeding grounds, as well as the female imagines entering rooms to partake of the blood meal essential for the transmission of the disease and the life-cycle of the fly.

Whittingham and Rook (1923[1]) carried out a series of experiments at Calafrana Camp (Map 2) in Malta to test the efficiency of various preventive measures. Their findings, stated briefly, were:-

I. WAR ON THE INSECT IN ITS VARIOUS STAGES.

(a) Abolition of breeding grounds by extensive repairs of cracks, and rendering surfaces impervious. This gave very good results, and in the treated area phlebotomus counts in huts fell by half.

(b) (i) Swatting.

Wet cloths proved to be the most effective swatters, and ladders were used to reach the insects in the higher parts of the rooms. A reduction in numbers of insects was achieved, but the method was laborious.

(ii) Spraying.

Cresol as an emulsion was found to be the best spray, and proved to be a useful weapon if carried out every two or three days.

(iii) Fumigation.

Formalin was satisfactory, but expensive and laborious.

II. PREVENTION OF BITING.

(a) Removal of hiding places in sleeping quarters by reduction of furniture and impedimenta kept by men in their huts reduced phlebotomus counts to some extent.

(b) Nets with 45 meshes to the inch were tried, and it was concluded that, "There was no doubt that nets, which were properly used and kept in repair, gave more protection than any other preventative."

(c) Repellents of which a number were tried, but their value was difficult to assess. The opinion formed was that paraffin and camphor were the most efficacious.

(d) Air Currents natural and artificial, were shown to have a considerable effect in reducing the numbers of phlebotomi in rooms. Owing to the greater air currents, sleeping quarters in upstairs rooms were found to be less infested by the flies than rooms at ground level. In the huts it was shown that the majority of flies was always found in the most secluded corners, depending on the direction of the wind.

Artifical air currents caused by small propeller fans in the corners of the rooms caused a considerable reduction in the flies in the higher levels, and large punkah fans gave good results in the lower parts of rooms.

Whittingham and Rook state "From a consideration of the above experiments (Fans) and of the effect of natural winds on phlebotomi, it is evident that, if properly used, electric fans afforded an excellent means of protection from the bites of these flies."

They gave the following summary of recommendations for a campaign for the prevention of sandfly fever.

SUMMARY OF RECOMMENDATIONS.

"To attain the best results concomitant with the minimum expenditure of labour and money, the prophylactic measures detailed above (in their paper - Whittingham and Rook 1923[1]) must be carefully planned and supervised. For the purpose of administration, these measures come under two headings:-

1. General (to be carried out by the community as a whole).

2. Personal (to be carried out by the individual).

1. General measures are to be preferred as they are more fully under control. All areas should be inspected at the end of the rainy season each year; this is, in the case of Malta, early in May. During the inspection, special attention should be paid to the following:-

(1) The ground surface, as regards levelling, impermeability and drainage.

(2) Buildings for cracks and holes and in the walls; ill fitting frames of windows, doors or ventilators; eaves gutters; holes in any fly-proof screens fitted.

(3) Walls and embankments, as regards necessary facing, pointing or tarring.

All the necessary repairs, tarring, painting and lime-washing must be carried out immediately before the warm weather sets in. Each year the interior of all rooms should be washed down and painted or lime-washed, the lower three feet of the walls of all buildings tarred, and the ground surface sprayed with tar for a distance of twenty feet beyond the living quarters. This last measure would not be required in a place where the ground surface around the building is covered with concrete.

2. The individual should see daily:-

(1) That the phlebotomi in the corners of their rooms are swatted, or sprayed with a 1 per cent. solution of cresol.

(2) That all rooms are thoroughly cleansed, especially the corners.

(3) That all cobwebs are removed.

(4) That ventilators are kept free from dirt, and are smeared with paraffin.

(5) That all gulley traps are kept clear.

(6) That the ground at the junction of walls of buildings is free from organic debris and dust.

(7) That all refuse is properly disposed of.

Further personal measures are:-

(i) To wear slacks after sundown.

(ii) Not to bathe after dusk.

(iii) Not to leave rubbish around or spill water on the ground.

(iv) To use sandfly proof nets 45 meshes to the square inch around their beds.

(v) To use repellents such as camphor in their beds.

Natural air currents must be fully utilised, and a liberal supply of electric fans or punkahs provided."

Discussion of Whittingham and Rook's Recommendations.

1. General. Extensive building and repair work requires labour and materials, and whilst it is justified in the case of a permanent establishment, can hardly be considered for temporary war-time premises. In Malta in 1945, neither the labour nor the materials were available.

2. Personal. Spraying and cleaning, to be done frequently, require labour which is not readily available for such tasks in war-time. The work involved in spraying with the insecticide sprays used prior to the introduction of DDT is well illustrated by the following quotation from Manson-Bahr (1945). "Flytox and Flit are the best sprays for destroying adult sandflies. Special staffs are necessary for the daily destruction of these insects in dwellings. Special apparatus is used and a flush of fluid is directed against the sandflies sitting on the walls or in corners. In hospital in an endemic area every ward and annexe, including latrines, should be treated with Flit three times a day."

Nets. The sandfly net provides good protection, and, if properly used and cared for, is very efficient. However, nets of such a fine mesh prevent circulation of air. In Malta, I found that on humid, still summer nights, sleeping in a sandfly net was very uncomfortable. In the summer heat of India it has been stated (Manson-Bahr, 1945) that such fine mesh nets may be found intolerable.

A specimen of sandfly net (net cotton 45/46 meshes to the square inch) and one of ordinary mosquito netting

(28/29 holes to the square inch) for comparison, are shown in figure 6.

Air Currents.

Whittingham and Rook proved the value of air currents, and since 1923, fans have been used extensively to prevent biting by sandflies. For fans, electric power is required, and fitting of large punkah fans requires time and labour. Again, the use of fans, whilst strongly advisable in a permanent establishment, is difficult to manage in an over-crowded temporary war-time one. In 1945, due to the shortage of electrical equipment, new fans of any type were not available.

Since 1923 little has been added to the preventive neasures. McArthur (1942) stated:-

> "Under active service conditions it is rarely feasible to make use of fine-mesh muslin as a measure of protection, to trap the adult flies, or to deal with breeding places. Spraying of tents, rooms, dug-outs, etc., may be feasible, and is likely to be of value. Tobacco smoke is useful. All that can be done is to employ repellents."

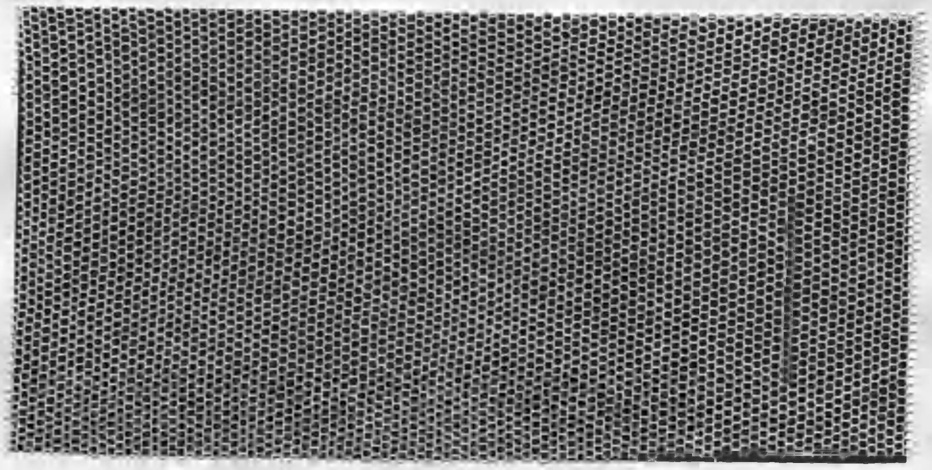
He also suggested the use of hurricane lamps smeared with vaseline or tanglefoot as traps for sandflies. But Young, Richmond and Brendish (1926) proved that light traps of this type caught few phlebotomi and were not likely to be of much use.

Rogers and Megaw (1939) have pointed out that all sandfly fever patients should be nursed under nets for

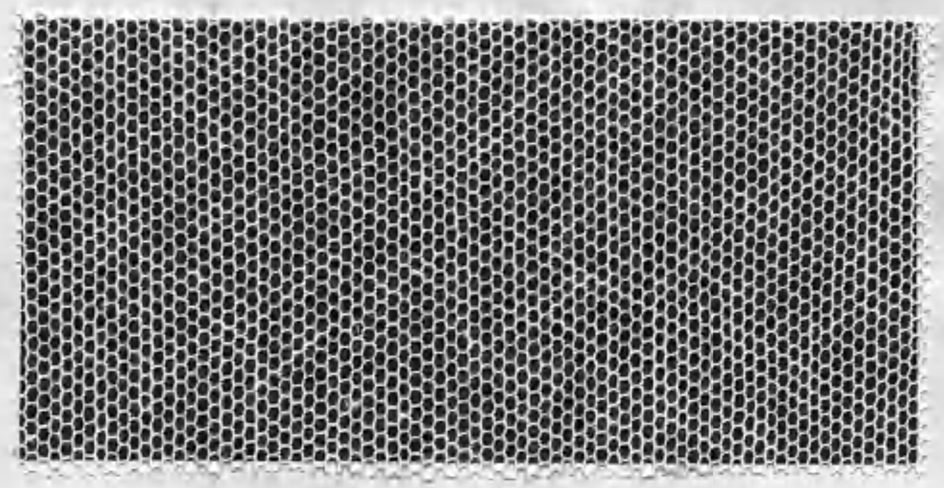
Figure 6.

Specimens of Mosquito and Sandfly Netting.

Sandfly Netting.
(45/46 meshes to the inch)



Mosquito Netting.
(28/29 meshes to the inch)



the first 24 hours at least, as hospitals may become hotbeds of infection.

Smith and his colleagues (1936) showed that Benzene Polychlorines, widely used in agriculture for the destruction of pests, were useful for the destruction of sandfly larvae when applied in liquid form in a strength of 75 c.c. to every square metre of soil.

Repellents.

In the past, a number of substances, such as camphor, paraffin, oil of citronella and mixtures of other essential oils, have been considered to be efficacious as repellents of phlebotomus flies. The multiplicity of substances recommended as repellents tends to suggest that none were very satisfactory.

Recently, a new substance, dimethyl phthalate, has been used. It is a clear liquid, colourless, odourless, and has no irritating effect on the skin. However, if the liquid gets on to the lips or is rubbed into the eyes, it is irritating and can cause considerable pain. Two cases of mild conjunctivitis have been seen from rubbing the eyes with fingers smeared with dimethyl phthalate, or D.M.P., as it is commonly called. This repellent was issued to the Services for use as a mosquito repellent in the anti-malaria campaign in the Pacific, but a limited amount became available in the Mediterranean in 1945.

Dimethyl Phthalate (D.M.P.).

Philip, Paul, and Sabin (1944) succeeded in obtaining direct evidence of the efficacy of D.M.P. in the prevention of sandfly fever.

In a barracks containing some 170 American soldiers on the outskirts of Cairo, the use of this repellent was the sole preventative measure employed during an epidemic period lasting five weeks.

Bottles of D.M.P., and distilled water, with or without a few drops of methylthionine chloride added, were supplied to men occupying alternate beds. Five cubic centimetres of repellent were used per man per day: this amount was applied in a thin film just before retiring, on the forehead, face, arms, hands, and other surfaces likely to be exposed during sleep.

The results were, 42 per cent. of those using the repellent reported relief from bites; of those using the control solution 12 per cent. reported relief.

Of the men who received the repellent, 2 acquired sandfly fever, but both admitted that they had failed to apply the repellent for several consecutive nights prior to contracting the disease. Of those receiving the control solution, 12 developed sandfly fever.

The same workers (Sabin et al. 1944[2]) also reported favourably on a pyrethrum vanishing cream used as a repellent. Pyrethrum has a repellent as well as a toxic effect on insects (Martindale 1936).

Experiments with Dimethyl Phthalate.

A. A simple experiment to observe the effect of D.M.P. on phlebotomus was carried out. Six sandflies were caught and put into a test tube, which was closed at the neck by a cotton wool plug. The test tube was left lying horizontal on the bench. At the end of half an hour, five of the insects in their efforts to escape had collected in the cotton wool.

The experiment was repeated with six phlebotomi, using a cotton wool plug to which three drops of D.M.P. had been added. For the first few minutes the insects became very active, but remained at the bottom of the tube as far away from the plug as possible. At the end of an hour, one phlebotomus was found on the cotton wool plug, and three moving about more freely in the tube, and the remaining two were dead.

B. The repellent was issued to the H.M. Dockyard Police (British) on night duty at the R.N. Hospital, as part of a general preventive measure to issue the repellent to all personnel on duty out of doors at night. These men, who had spent several summers in Malta, and on night duty, were enthusiastic about the repellent. A controlled experiment was not possible.

C. During August, 1945, H.M.S. AURORA was in the dry dock in H.M. Dockyard. The surroundings of this dock had been badly bombed and the area was heavily infested with sandflies. The weather was very hot and humid (Graph 2). Owing to the lack of electric power, the ventilation system of the ship was not working. Sleep was impossible below decks, so the men brought their bedding to the upper decks and slept there. They were very badly bitten and cases of phlebotomus fever started to appear. The issue of dimethyl phthalate brought relief from biting to most of the men. At first, several men reported no improvement, and it was found that they were not applying sufficient repellent. The repellent must be applied liberally (3 - 5 c.c.) to be effective.

The number of cases of phlebotomus fever also was greatly reduced, but this cannot be attributed to the D.M.P. Owing to the unsatisfactory conditions, arrangements were made to send contingents of the men on leave to Messina, and to billet others ashore in Malta. As a result, a much smaller number of men slept on the ship's decks at night, so fewer men were at risk after the issue of the D.M.P. than formerly.

D. Two officers slept on a verandah at the R.N. Hospital throughout the summer months, without the protection of sandfly nets. The verandah walls were sprayed with 5 per cent DDT (vide infra), and both applied D.M.P. on their faces, necks and arms nightly before going to bed. One officer received no bites, whilst the other was bitten once.

Whilst these experiments are inconclusive, they tend to support the view that D.M.P. is an effective repellent for Phlebotomus papatasii.

The prevention of outbreaks of sandfly fever is difficult, even in peacetime, but war conditions greatly add to the problem. In the past, in spite of painstaking preventive measures, the control of phlebotomus fever has not been entirely satisfactory.

The reported outbreaks in the Second World War had shown that the disease could still be a formidable nuisance in military operations. In 1945, conditions in Malta were favourable to test whether the new synthetic insecticide DDT, which had been used successfully in the control of other insect borne diseases, could control an epidemic of phlebotomus fever.

Section 2.

D D T. And Its Use Against Phlebotomus papatasii.

D D T.

DDT is a new insecticide which has been developed during the latter part of the recent war; it has received a great deal of publicity, and is now being extensively used. It is a powerful insecticide which kills a wide range of insects, and by its unusual property of prolonged residual insecticidal action has opened up new methods in combating disease.

HISTORY.

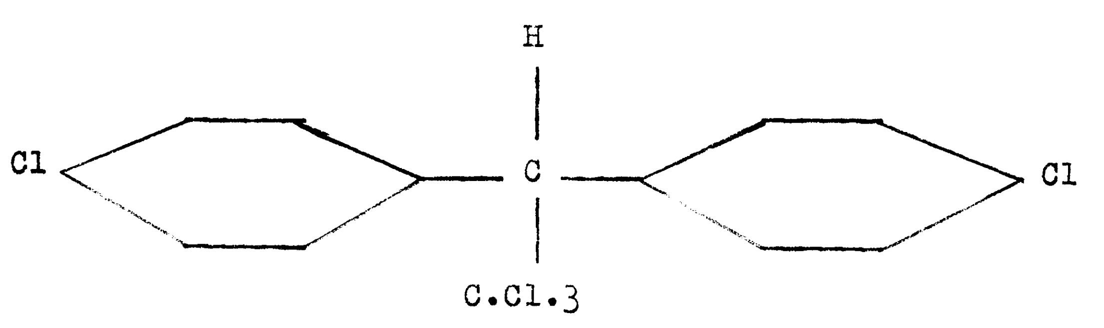
DDT was first synthetized by a German chemist Zeilder in 1874 by the action of chlorobenzene on chloral in the presence of concentrated sulphuric acid, a reaction which is the basis of present day manufacture, (Ministry of Supply, 1946). The Swiss firm J. R. Geigy, A.G., of Basle, investigated the substance, and it was found to have distinct insecticidal properties. As the firm was in search of a moth proofing agent which could be dissolved in dyes for application to textiles during the dyeing process, the poor solubility of DDT failed to make it suitable for this purpose. However, DDT was to some extent used as an anti-moth powder on the continent under the trade name of Gesarol.

In 1936 - 37, it was discovered by chemists of the same firm that DDT killed bugs, and it was also used successfully in 1940 to check a plague of potato beetles in Switzerland.

In 1942, the British Government was looking for a substitute for pyrethrum and derris, the two natural insecticides hitherto used against the insect vectors of malaria and typhus, (B.M.J., 1944, and Buxton, 1945). The supplies of these insecticides had been greatly reduced by the entry of Japan into the war. Buxton (1945) stated that the occupation of Malaya deprived the Allies of half the pyrethrum supplies and nearly all the derris; to make matters worse, the 1942 pyrethrum crop in Kenya was a poor one. DDT was produced as an alternative, and collaboration between the United Kingdom, Dominions and United States resulted in the production of DDT to meet the pyrethrum deficit, and in the development of the many aspects of its use. But DDT proved to be more than a substitute, in some respects it was superior to pyrethrum and derris. The Lancet (1945) stated, "Its chief virtues (apart from toxicity to insects) are chemical stability and physical inertia - in a word, its permanence. This contrasts with pyrethrum, which loses its insecticidal power rather easily in sunlight, especially when dispersed into small drops or thin films. On the other hand, DDT has one disadvantage in its slow speed of kill as compared with the rapid "knock-down" of pyrethrum."

GENERAL PROPERTIES.

DDT is dichloro-diphenyl-trichloroethane, or more correctly 1. 1 bis (p - chlorophenyl) - 2. 2. 2 trichloroethane, with a structural formula of



Pure DDT is a white crystalline substance with a molecular weight of 354·5 density of 1·6 gm per ml., and a melting point of 108° Centigrade. It is only slightly volatile and has a faintly pleasant smell. It dissolves in most organic solvents, though its solubility in water is very low, less than 0·2 parts per million (Buxton, 1945, and Ministry of Supply, 1946).

The pure substance is not used in actual practice, but a commercial product, which is now generally known as DDT. This DDT has a purity of 60 to 70 per cent. (Buxton, 1945, and Brit. Med. J., 1945), and is mixed with other substances, mostly isomers, which are only slightly insecticidal.

It is liable to contain small quantities of the substances used in its manufacture, e.g. monochlorobenzene and sulphuric acid. Both are undesirable for the former leads to a DDT which tends to cake and the latter to corrosion of the containers and dispersing machinery. These impurities can be removed by efficient washing and filtration (Ministry of Supply, 1946).

The specification for DDT used by the British Services requires a setting point of 89° C., containing not less than 70 per cent. pure DDT.

DDT is stable under most conditions, being unaffected by exposure to air, sunlight and water. It is almost insoluble in water, moderately soluble in petroleum and vegetable oils, depending upon the purity of the oils; and readily soluble in many organic solvents. The solubility varies with the temperature and the purity of the DDT.

In the present work kerosene was used as the chief solvent fot DDT. Crude kerosene can dissolve more DDT than refined kerosene.

Table 11.

Solubility of DDT in Some Common Solvents.
(Craufurd-Benson, 1945, and Buxton, 1945.)

Solvent	Solubility gms. DDT per 100 ml. at 27 - 30° C.
Kerosene, crude.	Approx. 8
Kerosene, refined, odourless.	Approx. 4
Acetone.	50 - 55
Ether.	27 - 28
Ethyl Alcohol 95%	Approx. 1·5
Dimethyl Phthalate.	31 - 33

SOLUTION OF D D T. IN KEROSENE.

The strength of DDT used in the present investigation was mainly 5 per cent. in crude kerosene. During the latter part of the epidemic period this mixture was supplied by the Naval Stores Officer already mixed, but at first, the DDT was supplied in solid form and the mixing was done at the R.N. Hospital, Malta, by the Pharmacist.

DDT does not readily dissolve in kerosene, and the usual directions for obtaining a solution are, to mix finely divided, sieved DDT powder into a cream by adding small quantities of kerosene. Then, to add this cream in small quantities to the main bulk of kerosene, which must be kept in motion by stirring or shaking. The containers should then be exposed to the sun in order to raise the temperature of the oil and thereby increase the solubility. To allow the DDT to dissolve, a period of about 3 days should elapse before using the solution.

The following rapid method of obtaining the solution of DDT in kerosene was promulgated by the Allied Force H.Q. of the Central Mediterranean Force, and proved to be most useful. The method is as follows:-

Melt the correct weight of DDT in a tin or bucket, at low heat, over a small flame or hot plate, and then pour the molten DDT into cold kerosene, stirring the latter all the time. Solution is immediate (e.g. 5 lbs. DDT slowly melted should be poured into 10 gallons of kerosene and briskly shaken. This gives a 5 per cent. mixture).

Care must be taken to melt the DDT over a small flame as the compound is volatile at high temperatures.

INSECTICIDAL PROPERTIES.

The mode of action of insecticides is still imperfectly understood. DDT is known to act as a poison when ingested by insects. It is absorbed from the trachea in the case of mosquito larvae.

It is also known that DDT acts on the nervous system, causing paralysis of the insect's legs and wings, incoordination of movement, twitchings, convulsions and finally death. The mode of entry of the insecticide is believed to be through the sensory organs in the tarsi in some cases, and in others by cutaneous absorption. West and Campbell (1946) giving an account of the researches carried out in the Basle laboratories of the Geigy Company, point out that the epicuticle, or outermost layer of cuticle in insects consists of lipoids which keep the insect to some extent waterproof. They propound the current theory that DDT (and other contact insecticides like pyrethrum and derris) dissolve in the lipoids of the epicuticle and then exert a toxic action firstly on the sensory nerve endings in the epicuticle and later on the central nervous system of the insect.

Busvine (1945), as a result of investigations on lice and bugs, has been unable to find any evidence to support this hypothesis of lipoid solubility of the toxic factor of DDT.

Yeager and Munson (1945), who have investigated the site of action of DDT in cockroaches, have suggested that the insecticide can affect motor nerves more readily than sensory ones, and that the site of action would appear to be somewhere along the length of the nerves and not at the origin of the nerves or at the nerve endings. Further, that DDT can cause tremors by exciting impulses in the motor nerves.

At present, with the imperfect state of our knowledge, no satisfactory theory of the mode and site of action of DDT has yet been formulated.

The important point is that DDT is both a stomach and a contact poison. In the latter instance, it acts on the nervous system.

The insecticidal action is slow and takes from half an hour to four hours to kill flies, six to eight hours to kill lice, and much longer for bedbugs and cockroaches,

Owing to the slow action of DDT. insecticide sprays are often made up of a rapid acting poison, such as pyrethrum and DDT. The pyrethrum gives a rapid 'knock-down' effect, and the slow acting DDT ensures death, thus saving pyrethrum. The British Service Anti-Mosquito Spray (0·5 per cent. DDT and 0·03 per cent. pyrethrins in kerosene) used as a flit was, in my experience, effective for clearing a room of winged insects. It had no apparent residual action.

Experiment has shown that when attacking insects with DDT, an actively flying insect more rapidly picks up a toxic dose than a quiescent one. A small quantity of pyrethrum is sufficient to activate an insect and consequently leads to an effective kill. Therefore, even when the ultimate kill is the chief concern, and DDT is used as the main agent, the addition of a small amount of pyrethrum has advantages (Ministry of Supply, 1946).

DDT is not a repellent to insects, and it is not ovicidal. In general, it does not attack pupae, though frequently the adult may pick up a lethal dose during emergence. In some cases, e.g. the mosquito, it attacks the larval stage.

ACTION OF D D T. ON P. PAPATASII.

The following experiments were made to ascertain the action of DDT on P. papatasii. The insects were caught in the wards and balconies of R.N. Hospital, Malta, by searching for them on the walls, then placing a wide diameter test tube over the fly. A visiting card was then slipped between the wall and the test tube; the insect removed and gently shaken down the tube. The mouth of the tube was closed with a rubber stopper. It was found that if cotton wool plugs were used, the sandflies frequently got entangled in the cotton wool and died. With a little practice it became fairly easy to catch phlebotomi in this way during May and June, 1945 (i.e. before extensive spraying with 5 per cent. DDT.)

Experiment 1:-

A glass jar was sprayed with 5 per cent. DDT in kerosene and allowed to stand in the air for 3 days. Three phlebotomi were put in the jar and the mouth of the jar was closed with a sprayed glass cover. Within three minutes the three insects were lying at the bottom of the jar, and after ten minutes when the cover was removed, the phlebotomi were found to be dying - occasional twitchings were observed up to half an hour.

To make observation easier, the jar was gently dusted out so that the white crystalline deposit of DDT on it could no longer be seen. Ten sandflies were put into the jar and the lid fixed in position. At first, the flies made efforts to escape, crawling up the side of the jar and over the lid. At the end of ten minutes, all the flies were at the bottom of the jar, and by half an hour they were dead. At the same time, as a control, six flies in a clean untreated jar were kept overnight, and in the morning only two phlebotomi were found to have died.

The experiment was repeated with a further eight phlebotomi, after the inside of the jar, which had been sprayed with 5 per cent. DDT, had been wiped for a second time, with a clean dry duster.

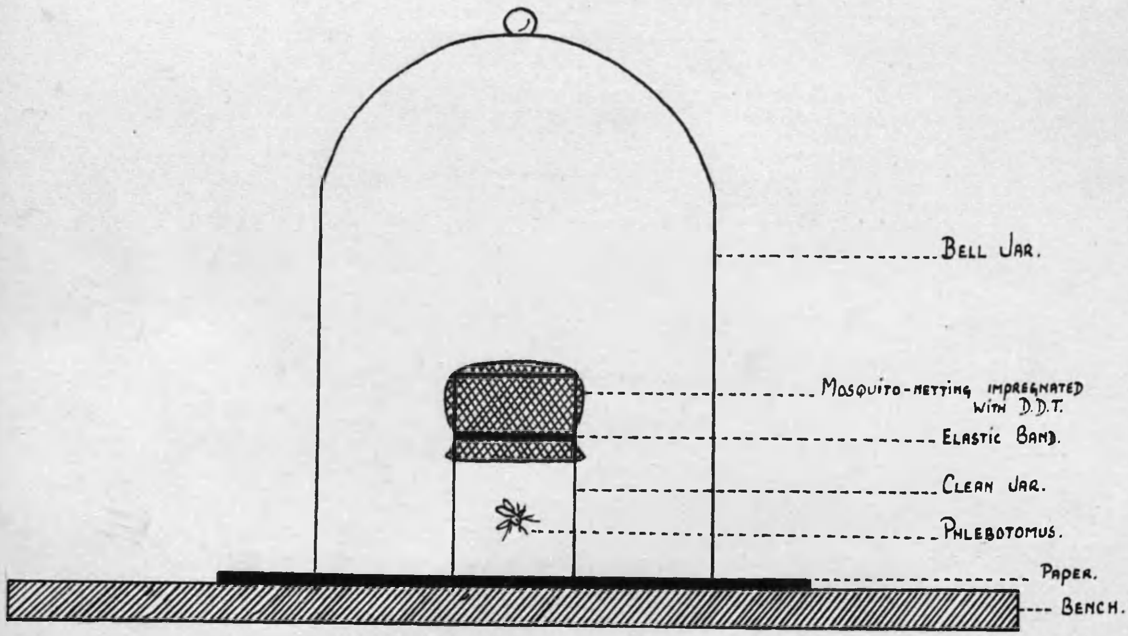
At first, the insects crawled up the sides of the jar and made efforts to escape. By the end of half an hour the flies were all at the bottom of the jar, and were showing signs of incoordinated movements. After two hours all the phlebotomi were dead.

These results are substantially in agreement with the findings of Hertig and Fisher (1945), who carried out laboratory tests in Italy. They showed that contact with DDT caused a 'knock-down' of P. perniciosus and P. parroti in 6 to 15 minutes, while P. papatasii required 15 to 40 minutes.

Experiment 2:-

A sandfly was placed in a clean glass jar, (Figure 7) and the mouth of the jar covered with a piece of mosquito netting which had been soaked in 5 per cent. DDT in kerosene and thoroughly dried. The jar with the mosquito netting held firmly in position by an elastic band was then placed underneath a bell jar. The fate of the insect was

Figure 7.



Apparatus for testing the effectiveness of mosquito-netting impregnated with DDT as a phlebotomus barrier.

observed.

This experiment was carried out fifteen times, with the following results:-

(a) 2 phlebotomi made no attempt to escape, and died at the bottom of the jar.

(b) 6 phlebotomi crawled over the mosquito netting, but failed to penetrate it. At the end of one hour four of the flies were dead, adhering to the netting. The other two were found lying dead at the bottom of the jar after four hours.

(c) 6 phlebotomi managed to penetrate the netting, and after one hour 3 were found on the netting, two of which were still twitching. Three of the remaining insects were found on the paper placed beneath the jar on the bench; two were dead but one was still twitching.

(d) 1 phlebotomus which was observed on the mosquito netting was not seen again.

Experiment 3.

Whilst the above experiments were being carried out, a shortage of sandfly nets occurred at the R.N. Hospital, so ten patients on one of the balconies were supplied with mosquito nets which had been sprayed with 5 per cent. DDT in kerosene. The nature of the investigation was explained to the men, and they were asked to make a special note if they were bitten during the night and report it in the morning. Ten patients slept under these impregnated mosquito nets from the 2nd June till the 4th July, 1945, and only two men reported one insect bite each, which may or may not have been due to phlebotomi. The balcony was sprayed with DDT on the 4th July, and the experiment was abandoned. Unfortunately, no control series was done with men sleeping in unimpregnated mosquito nets. The balcony was definitely infested with sandflies as many of the insects for the above experiments were caught there; also the night staff in the adjoining ward were frequently bitten. The unimpregnated mosquito net is known to be ineffective as protection against sandflies.

Conclusions.

(i) Phlebotomus papatasii is susceptible to the toxic action of DDT, and contact with the insecticide fairly rapidly renders the insect incapable of biting and eventually kills it.

(ii) Mosquito nets impregnated with DDT form an effective protective barrier against phlebotomus flies. This will allow the replacement of the uncomfortable close mesh sandfly net by an impregnated mosquito net, resulting in greater comfort during sleep in hot phlebotomus infested areas. In many of these areas, as malaria is also endemic, some net protection will be required in addition to wall spraying with DDT.

METHODS OF USE OF D D T.

In practice, undiluted DDT is not used. The diluted insecticide is used in a number of different ways in order to deal most efficiently with each particular insect control problem. The following preparations are now in common use, Dusts, Emulsions, Suspensions, Solutions and Aerosols. DDT is also effective mixed with distemper or oil-bound water paint (Campbell & West, 1944).

A. Preparations.

(a) Dusts.

The DDT is mixed with an inert vehicle, such as China Clay. The common dusts in use are the Services A.L.63, Mark iii, which consists of 5 per cent. DDT in 95 per cent. China Clay, and A.L.63, Mark iv, which is 10 per cent. DDT in 90 per cent. China Clay.

These dusts are mainly used against lice, and reports are now available of their efficiency in the control of typhus outbreaks, especially in the epidemic at Naples in 1943 - 44, and in the concentration camps in Germany in 1945, (Craufurd-Benson 1946, Chalke, 1946).

The dust is usually applied by means of hand or power operated dust guns, and by this means de-lousing of fully clothed individuals can be carried out.

The dusts may also be used as larvicides in mosquito control.

(b) Emulsions.

These have the advantage of not requiring large quantities of solvents. The DDT is dissolved in an organic solvent, then mixed with an emulsifier (e.g. soft soap). The resultant DDT concentrate can then be diluted with water to the required strength. Emulsions may be used as sprays similar to solutions. Emulsions have not the same solvent action on rubber as oil solutions and, therefore, do not cause hoses and washers to perish. However, they may cause corrosion of the spraying apparatus, (Ministry of Supply, 1946).

(c) Suspensions.

Suspensions are made by using a wetting agent such as sodium lauryl sulphate, or soft soap. The DDT tends to settle out, and suspensions are mainly used in mosquito control for larviciding.

(d) Solutions.

Solutions of DDT are the most effective owing to the better distribution obtained. These are prepared by dissolving DDT in a suitable solvent. For work in the field, kerosene is the solvent most used.

Two solutions have been issued for use by the British Services -

1. Anti-Mosquito Spray, which consists of:-

DDT .... 0·5 per cent.
Pyrethrins .... 0·03 per cent.
Kerosene (+ Sesame Oil 5 per cent) to 100 per cent.

2. Residual Spray, which consists of:-

DDT.............................. 5 per cent.
Kerosene (Crude) .... 95 per cent.

The Anti-Mosquito spray, when dispersed as a fine mist produced by a 'flit-gun', quickly clears rooms or tents of winged insects. The pyrethrins cause an immediate 'knock-down' of the insects and the DDT kills them in due course.

The Residual Spray is the solution commonly used for wall spraying, and was used in the present investigation to control phlebotomi.

(e) Aerosols.

A concentrated insecticide solution dispersed by fine atomisation is the most effective method of using a spray against adult insects.

DDT dissolved in a mixture of non-volatile solvent and low-boiling solvent is allowed to escape into the atmosphere under the pressure of the low-boiling solvent. The latter evaporates instantaneously, leaving a very fine mist of the non-volatile solvent (Ministry of Supply, 1946). DDT has been used in an American aerosol bomb, and has been found to be effective, both against flies and mosquitoes, but the Freon used as the low-boiling solvent was not satisfactory and allowed clogging of the nozzle with DDT. However, by replacing the Freon wholly or in part with methyl chloride this difficulty has been overcome (West and Campbell, 1946).

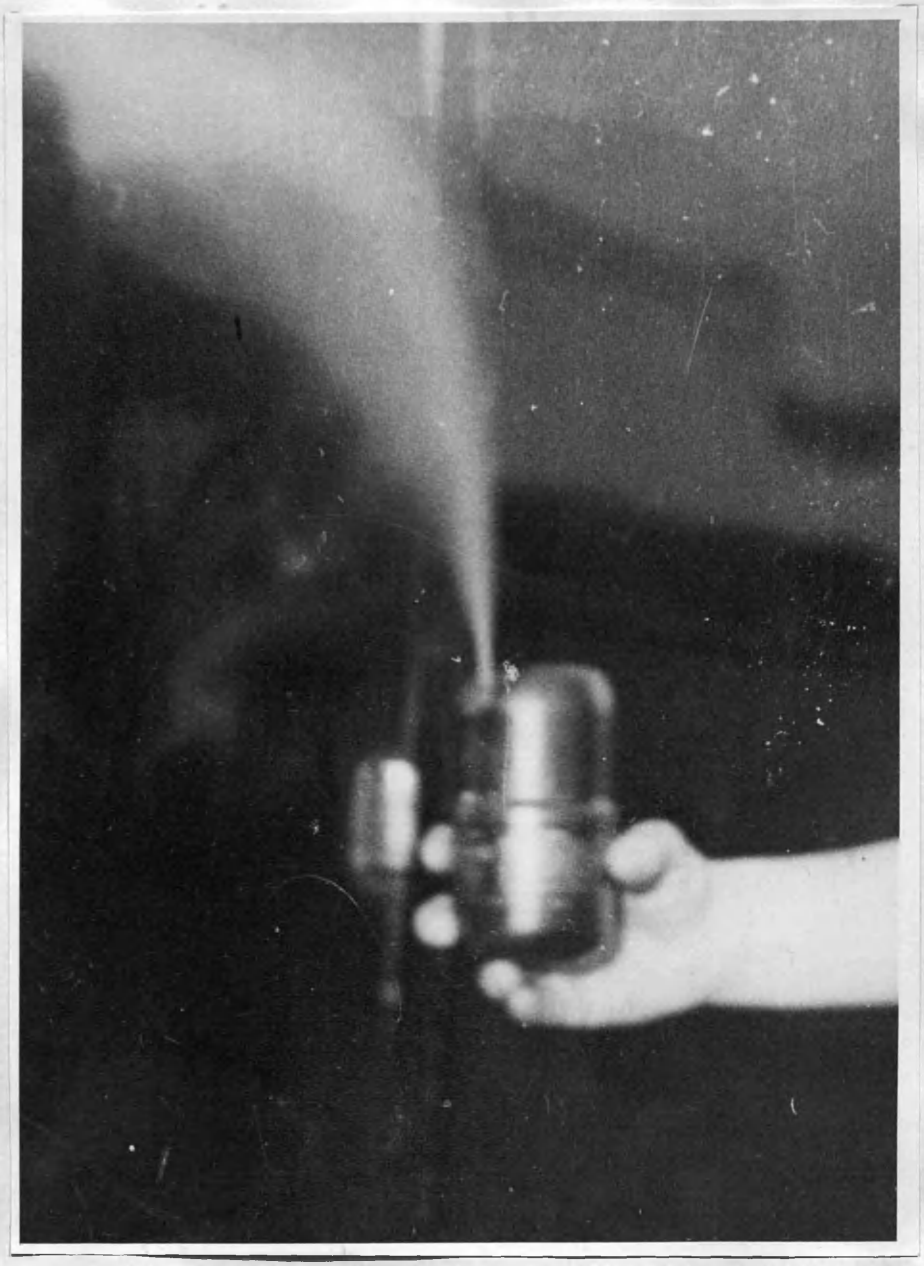
I had no opportunity to test the DDT aerosol bombs, but had experience with the U.S. Westinghouse aerosol bomb (Photographs I and II). This bomb weighed 26 ounces loaded, and contained 18 ounces of insecticide (0·4 per cent. pyrethrins in 6 per cent. sesame oil) and the propellant Freon 12 (dichlorodifluoromethane). Four seconds spraying with this bomb was said to disinfest (for flies and mosquitoes) 1,000 cubic feet. Each bomb contained enough insecticide for 15 minutes continuous spraying.

Photograph 1.

Westinghouse Aerosol Bomb.
(in action)

Photograph 11.

Westinghouse Aerosol Bomb.
(in action)



The bomb was found to be most effective against flies, mosquitoes and sandflies. It provided a pleasant means of getting rapid clearance of winged insects from rooms.

The British Service Individual Insecticide Sprayers (Sparklets) were somewhat similar to the above. Pyrethrum was the insecticide used, but the propellant was carbon dioxide (CO_2).

Recently investigations on the dispersal of DDT in smokes have been in progress. This work is still in its early stages, (Ministry of Supply, 1946).

(f) Impregnation.

The impregnation of clothing with DDT has been successful in the prevention of louse infestation. The issue of impregnated shirts during the latter part of the recent war greatly reduced body louse infestation amongst the troops.

B. Wall Spraying:-

Because of its great stability, DDT has a pronounced residual effect which is unequalled by other insecticides. Therefore, if the substance is deposited on surfaces whether as a dust, an oil solution, or an emulsion, it leaves a coating of DDT which exerts, for several weeks at least, a lethal effect on insects coming in contact with it.

Formerly, insecticide liquids contained mainly pyrethrum (Flit, Flytox, etc.). They were dispersed in rooms as fine mists because it was necessary for pyrethrum to come into contact with the insects before its toxic effect was destroyed by the oxidising action of sunlight and the atmosphere. Such insecticide sprays had no residual effect.

The principle of wall spraying is entirely different. It is to cover surfaces with a fine film of DDT, and as a result of the residual action of DDT insects landing on these surfaces and remaining in contact long enough will absorb a toxic dose.

As a result of the trials carried out by the Insecticide Development Panel of the Ministry of Production, a 5 per cent. concentration was found to be satisfactory for most purposes and was recommended for use by the British Services.

The 5 per cent. Residual Spray with kerosene as the vehicle was used in the present investigation.

It is probable that a smaller concentration of DDT would have given similar results in the control of sandflies, but this spray, in addition, dealt effectively with flies and mosquitoes. It also kept the naval establishments practically free of cockroaches, bedbugs and other insect pests.

The insecticidal action of DDT after spraying has been stated to last for from two to three months (Lancet 1946); this, of course, will vary with the concentration of spraying, and the climatic conditions in the area. In Malta, dead insects were found three months and even longer after a single treatment. The period of effectiveness of two to three months would seem a reasonable figure for Malta.

C. Dosage of Residual Spray.

Field experience in Italy, India, Assam, New Guinea and West Africa, had shown that 50 - 100 mgm DDT per square foot (i.e. 1 - 2 c.c. per square foot of 5 per cent. spray) was effective up to two months after application (Craufurd-Benson, 1945).

Buxton (1945) recommended 100 mgm per square foot as the dose to be aimed at.

Hertig and Fisher (1945) carried out field trials in Palestine to test the effectiveness of DDT in the control of sandflies. 5 per cent. DDT in kerosene was sprayed on the insides of buildings at the rate of 1 to 1·5 gallons per 1,000 square feet (i.e. 224 mgm DDT per square foot). The results as judged by fly counts and the reports of the inhabitants of the houses indicated that almost complete control was obtained. Spraying only round the doors and windows of rooms led to a reduction in the fly counts to a quarter of their former level, and few bites were reported.

These workers recommended that for practical control of sandflies, the entire inside walls and a part of the ceiling should be treated, as well as the outside margins of windows and doors. Their dosage of DDT was a very heavy one, and in comparison with the present investigation would appear to be excessive.

In Malta, the 5 per cent. Residual Spray was applied in a dose of 1 quart per 1,000 square feet (i.e. 56 mgm DDT per square foot). The spraying parties were taught to apply the liquid so that it just "wetted" the wall. It was found that with a little practice the spraying team became efficient at this. A check was made of each spraying party in rooms where the approximate areas sprayed were ascertained. Generally the figure worked out just a little above 1 quart per 1,000 square feet. This allowed for wastage. With this dosage, near perfect control of sandflies indoors was obtained.

D. Methods of Residual Spraying.

Residual spraying required a spray which would apply an even adherent coating of the liquid on the surfaces sprayed. Also, the spray had to be such that the insecticide liquid did not splash off the wall and fall to waste on the floor.

Power sprays working with compressed air similar to the paint-guns used in industry were known to have given excellent results in North Africa. They were economic with the liquid, as well as time and labour saving.

In Malta in 1945, power sprayers were not available, and other methods had to be used. Two sprayers were used.

(a) <u>Stirrup Pump Sprayers.</u>

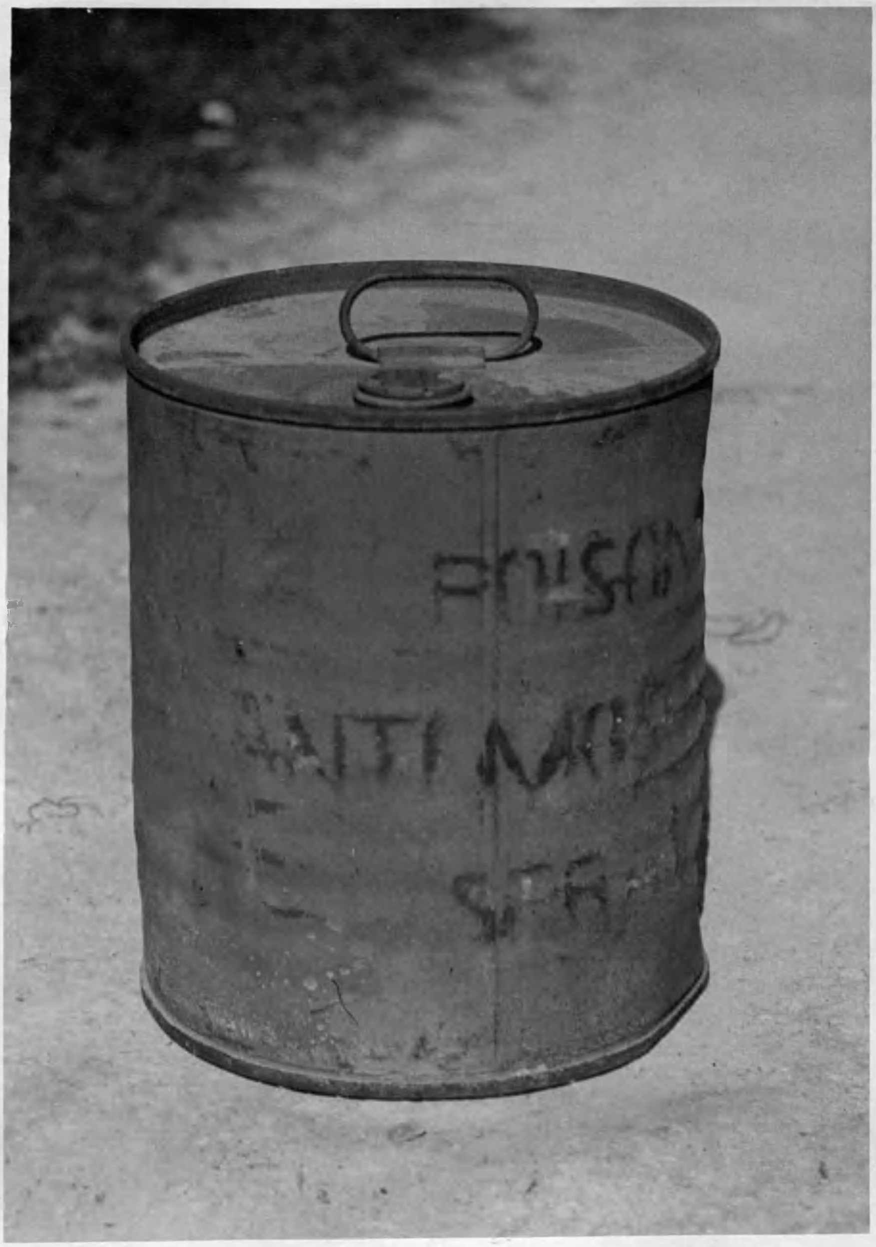
These were the ordinary stirrup pump which was used for passive defence purposes. When the scheme for wall spraying was being prepared, it was learnt that no sprayers were likely to arrive from U. K. in time to deal with the anticipated phlebotomus fever outbreak, so an improvised sprayer had to be devised.

The stirrup pump was taken, and a new nozzle was produced by the Engineering Department of H.M. Dockyard, with a jet of one sixty-fourth of an inch (1/64"). This size of jet had been found best for spraying in Italy by Craufurd-Benson (1944). The problem with such a fine jet was that it tended to clog easily, so the Engineering Department arranged for the new nozzle to be easily dismantled to allow for rapid cleaning by the spraying teams.

At first, fire buckets were used for the Residual Spray, but later, when the liquid was supplied in four-gallon drums from Egypt, the stirrup pump was inserted into the bung-hole of the drum, and this resulted in a considerable saving of liquid, (Photograph III).

Photograph 111.

Four gallon insecticide liquid drum.



The stirrup pumps, of which there were large stocks in the Naval Stores, were satisfactory only as improvised sprayers. They leaked at the nozzle, and were wasteful; after about a week of use, the rubber hosing perished and burst as a result of the action of the kerosene. Each stirrup pump required two men, one to pump and one to do the spraying. Yet, in spite of all these shortcomings, the stirrup pumps did a reasonably efficient job. They were not used as apparatus of choice, but as improvisations in an emergency.

(b) Knapsack Pressure Operated Sprayers.

Among the Naval Health Officer's anti-malarial stores were twelve Four Oaks "Kent" Sprayers, which had been supplied for spraying oil on water for killing mosquito larvae. These sprayers were the type frequently used by gardeners for spraying fruit trees. For wall spraying DDT Residual Spray, they gave excellent results.

The Four Oaks Sprayer was a one man unit, (Photographs IV and V). The power for operating the spray was provided by the compressed air in the container which was pumped in by means of the hand pump prior to starting to spray. Although the pressure in the sprayer could be pumped up to 70 lbs. per square inch, experience showed that high pressures led to splashing and wastage. The sprays were used between 10 and 30 lbs. per square inch, which gave the best results. This entailed two to three pumpings to every filling of the container.

It was discovered that these sprayers soon

Photograph lV.

Four Oaks "Kent" Spray.
Used for wall spraying.

Photograph V.

Four Oaks "Kent" Spray
in action on an embankment wall
at R.N. Hospital, Malta (note the crevices).
It is a one-man unit. The brass extension
rod allows the operator to keep clear of the
spray.

leaked if not cared for. The kerosene rotted the leather washers, and the apparatus became inefficient. However, when the sprayers were emptied and blown through with air to dry them after use, this trouble ceased. The spraying teams were quick to learn this, and with proper care, the Four Oaks Sprayers gave good service.

A supply was ordered for 1946, and I have been informed that they have been extensively used, and have continued to prove a good type of one man unit.

E. Spraying Organisation, 1945.

The naval establishments in Malta were divided into five groups. One establishment within each group was made an Anti-Sandfly Headquarters, and to it was attached the Anti-Sandfly Squad. Each squad consisted of the Senior Medical Officer of the area, an Officer, two Petty Officers and ten ratings. The Officer and the Petty Officer were permanent members of the squad, but the ratings were constantly changing. Mainly, ratings in transit were used.

The Officers and Petty Officers were given intensive instruction on the control measures to be taken against sandflies. They were issued with the apparatus, and several practices were held. At first, weekly conferences were held in order to give everyone a clear understanding of what was required. The delay in the DDT arriving in Malta, though disappointing, provided an ample opportunity for bringing the Anti-Sandfly Squads up to a high degree of efficiency and enthusiasm.

Protective clothing was not worn by the

spraying teams (vide infra.), and the chief hazard was considered to be the danger of fire. Smoking was not permitted in rooms in which spraying was in progress, and arrangements were made for spraying galleys when the fires were out.

The main duty of the Officer was to arrange the spraying programme of each squad to fit in with the other requirements of the various establishments. He also generally supervised the work. The Petty Officers trained and supervised the work of the ratings, and were constantly present during spraying.

The first spraying was done between the 22nd June and the 6th July, and at six to eight weekly intervals thereafter.

The effect of the first spraying was dramatic, sandflies practically disappeared from rooms and dormitories, and the fly nuisance was greatly reduced. The large numbers of dead flies swept up daily provided visual proof of the effect of DDT. From then onwards, the difficulty was to limit the spraying of naval establishments to six weekly intervals. This was essential as supplies of the insecticide were limited.

TOXICOLOGY.

Much research work has been carried out on the toxicity of DDT to man, the higher animals (especially farm animals), and the various lower forms of life beneficial to man (e.g. fish). Apart from the importance of establishing how poisonous the new insecticide was prior to its being accepted for extensive use, Bishopp (1945) has given another interesting reason. Late in 1942, a sample of DDT was sent by the Geigy Company to its American branch. Initial tests were conducted with caution, since the material appeared to be a nerve poison, and it was suspected that possibly Germany had permitted the material to be shipped out of Switzerland in the hope that it might be used extensively on American troops and in some way adversely affect them.

Extensive tests have been carried out in this country by Cameron and Burgess (1945), and in the United States by Draize, Nelson and Calvery (1944); Woodward, Nelson and Calvery (1944); Smith and Stohlman (1944); and Lillie and Smith (1944). Some observations have also been made in West Africa by Hill and Robinson (1945).

As the results of these workers are substantially in agreement, no attempt will be made to review them in detail. The following is a summary of their main findings in animal experiments:-

(a) Repeated exposure to moderate doses of DDT appears to be more dangerous than exposure to a single large dose.

(b) The chief effects of a single large dose are coldness, tremors, muscular weakness, incoordination of movements, anorexia with rapid wasting, and, eventually, respiratory paralysis and death. The signs of intoxication which appear in 12 to 24 hours may disappear again within a few days with complete recovery.

To produce a fatal result, relatively large doses are required. For instance, the L.D.50 (median lethal dose) for rabbits was estimated to be 300 mgm/kgm. body weight (Smith and Stohlman, 1944), using 1 to 5 per cent. DDT in olive oil given by the stomach tube. Hill and Robinson (1945) estimated the L.D.50 for baboons as between 236 and 472 mgm/kgm., using 5 per cent. DDT in kerosene given by the stomach tube. For skin application of single doses, Cameron and Burgess (1945) found the L.D.50 for rabbits was 300 mgm/kgm., for guinea pigs 1,000 mgm/kgm., and for rats 3,000 mgm/kgm., using DDT dissolved in medicinal liquid paraffin.

When death occurs after the exhibition of a single large dose of DDT, the pathological findings are not marked. Pulmonary oedema may be present as a terminal manifestation. Mild or moderate damage of the liver and kidneys similar to that found after repeated administration may be found, but is not constant. Cameron and Burgess (1945) have confirmed the finding of the American workers (Smith and Stohlman, 1944, and Lillie and Smith, 1944) of degenerative changes (chromatolysis, tigrolysis, vacuolation, pyknosis) and sometimes destruction of a few anterior horn cells in the thoracic and lumbar regions of the spinal cord.

(c) With repeated administration of moderate doses of DDT a more definite clinical and pathological picture emerges. There is loss of weight, anorexia, mild anaemia, with polymorphonuclear leucocytosis, and damage to the central nervous system, causing excitability, instability, tremors and muscular weakness. The main pathological features seem to be liver damage, which in its mildest form consists of cloudy swelling with fatty degeneration, but may go on to numerous areas of focal necrosis or large areas of centrolobular necrosis which are uniformly distributed throughout the organ.

Cameron and Burgess (1945) found that calcification sometimes occurred in the necrotic areas. They discovered necrotic changes to a lesser degree in the kidneys. They also reported that in rabbits exposed to large skin doses there was evidence of a rise in blood calcium values.

Toxicity to Man.

Cameron and Burgess (1945) made some observations on human subjects, (1) wearing undergarments impregnated with DDT, and (2) working in contact with DDT. They concluded that there was little risk of local skin irritation or general systemic effects attributable to DDT, even with prolonged exposure. In many of their experiments, there were ideal conditions for absorption from hot sweaty skin.

Wigglesworth (1945) reported a case of DDT intoxication in a laboratory worker who had been in daily contact with high concentrations of DDT in acetone and in powder form far in excess of the concentrations likely to be met with in the routine use of the compound in insecticide work.

The clinical syndrome was heaviness and aching of the limbs, sleeplessness, "spasms of extreme nervous tension", prostration of such a degree as to confine the sufferer to bed for a fortnight, and involuntary muscular twitchings of the whole body on at least three occasions.

At the end of a year, full recovery had not taken place.

As Case (1945) states, "This report of Wigglesworth's is of great importance in that it removes the question of human DDT intoxication from the sphere of theoretical speculation to the realm of industrial medicine; for it is likely that a substance known to be toxic to mammals, shown to be toxic to men under certain conditions, and in wide use may produce subclinical manifestations, not at present recognised, which will lower the health-level and efficiency of workers at risk, and that the rapidly growing use of DDT will extend into circumstances where human intoxication is likely to occur."

Case (1945) investigated the possible toxic effect of a distemper containing 2 per cent. by weight of dry film of DDT. He exposed two subjects for 48 hours under special conditions (oily wall surfaces, large skin areas exposed, high ambient temperature and relative humidity) in a compartment which had been treated with the distemper. Definite toxic effects were produced, including an increase of erythrocyte destruction (siderocytosis), a decrease in the mean corpuscular haemoglobin, and a diminution of polymorphonuclear leucocytes. This last observation is at variance with the findings in animals of Cameron and Burgess (1945), who considered that a rise in the white cell count with an absolute polymorphonuclear leucocytosis might be a sign of diagnostic importance. The chief subjective phenomena noted were tiredness, heaviness and aching of the limbs, diminution of some reflexes, muscular weakness of the legs, and an apprehensive mental state.

He stressed the danger of DDT causing intoxication, particularly in the presence of oil.

Hill and Robinson (1945) (and Hill, 1946) have described a fatal case of DDT poisoning in a child aged 1 year 7 months. This is the only human fatal case so far recorded.

The child (a West African) drank about 1 ounce of a solution of 5 per cent. DDT in kerosene. Shortly afterwards he vomited, but gradually worsened, and in an hour and a half became comatose, had convulsions which appeared to consist of generalised fine tremors. He died four hours after drinking the liquid. At the post-mortem examination, there was some congestion and oedema of the brain. There was little of significance in the viscera and the cause of death was pulmonary oedema. This pulmonary oedema was stated to be probably due to paralysis of the respiratory centre.

These workers carried out control experiments with baboons, and have claimed to show that the child's death was due to DDT poisoning and not to the kerosene.

It may be concluded from the foregoing data that DDT is no more toxic than many insecticides and other substances in common use, but it should be handled with care to avoid ingestion and prolonged contact of oil solutions with the skin.

Toxic levels are not easily reached when dilute solutions suitable for insecticidal purposes are employed. Danger to health is likely to arise only from the careless use of concentrates, (Cameron and Burgess, 1945). DDT used as an insecticide would appear to be quite safe.

Personal Observations.

During planning of the residual spraying campaign for the control of phlebotomus fever in 1945, it was decided that the men using the sprays should be protected against heavy skin contamination with the oily solution and also against inhalation. Whilst the hazard was not considered to be great, it was known that Draize and his co-workers (1944) had shown toxic effects occurred in animals from applications to the skin of oily solutions containing DDT. Also, that Neal et al. (1944), who studied the hazards from the use of aerosols, mists and dusting powders containing DDT in dogs, rats and guinea pigs, had found that intoxication and death could occur with very high concentrations. Protective clothing was issued to the spraying teams in the form of oilskin coats, oilskin anti-gas gauntlets and surgical face masks. In this planning, I had overlooked the heat of the Mediterranean summer. Wearing the protective clothing, any physical effort was tiring, and slow progress with the spraying was made. After the first few days the protective clothing was withdrawn and the men worked in shorts and shirts. The Petty Officers in charge of the teams were instructed to see that the men washed their hands and arms thoroughly before dinner and at the end of the day's spraying. They were told to look out for any signs of unusual lassitude among their teams and to report immediately any skin rashes. During the whole summer not a single man from any of the spraying teams developed any symptoms which might have been due to the toxic action of DDT. Nor was any irritation of the skin due to the oily solution reported, although it was being specially looked for, and all personnel were told to report a skin rash immediately. The spraying teams got their hands and arms heavily contaminated with the oily solution owing to the improvised stirrup pump sprayers, which all leaked to some extent.

One factor which must not be overlooked is that the personnel of the spraying teams was constantly changing, and only a few men were on the job daily for more than three to four weeks. The Petty Officers, who were permanent, did not come into such close contact with the Residual Spray.

Case Report of Skin Eruption

due to 5 per cent. DDT Residual Spray:-

During the summer of 1945, there was an outbreak of bubonic plague in Malta, and the effectiveness of DDT as a measure for destroying the vector, namely the rat flea (Xenopsylla cheopis) had been given considerable press publicity. As a result, a Maltese dockyard workman, on the afternoon of 31st August, finding a spraying outfit unattended, put the nozzle of the sprayer up each trouser leg and thoroughly sprayed his legs and the inside of his trousers with Residual Spray. The reason he gave was to prevent fleas biting his legs and to protect him from plague.

On retiring that night he noticed some smarting of his legs, but saw no rash, but next morning when he got out of bed he found both legs covered with a rash up to his groins. He reported the rash to his foreman on arrival at the dockyard, and was sent to the R.N. Hospital.

Examination.

When seen at 09.30 on the 1st of September, an eczematous rash was seen on both legs and thighs, extending from just above the ankles to the groins (photograph VI). The rash was hot and itching; several small areas of vesication were seen in the popliteal regions. The eruption was most marked round the knee.

The man stated that he had never had any skin rashes previously, and he did not suffer from asthma. His job in the dockyard was that of a Fitter, which he had worked at for 14 years. He frequently came into contact with oil and grease at his work.

In order to ascertain the true cause of the eruption, a series of patch tests (photograph VII) were carried out on the dockyard workman, and on a medical officer who volunteered for the experiment.

Three patch tests were done on both subjects:-

(a) Proximal Test.

A piece of lint (about 1½ inches square) soaked in 5 per cent. DDT Residual Spray, was well wrung out, placed on the arm and strapped in position with adhesive plaster.

(b) Middle Test.

A similar piece of lint was soaked in a saturated solution of DDT in ether. This was not wrung out but allowed to dry in the sun, then applied to the arm as before. This

Photograph V1.

Eczematous rash on limbs, 44 hours after application of Residual Spray.

Photograph V11.

Patch Tests.
Appearance after 24 hours.

(a) Residual Spray
(b) DDT.
(c) Kerosene.

Control. Medical Officer.

Patient. Dockyard-man.

(a) (b) (c)

(a) (b) (c)

was to test whether either subject was sensitive to DDT.

(c) Distal Test.

A similar square of lint was soaked in kerosene. The lint was wrung out, applied to the arm and fixed in position with strapping. This was to test sensitivity to the crude kerosene solvent.

The proximal and distal tests showed a marked reaction with vesication in both subjects, whilst the middle test in both gave no reaction. This proved conclusively that the rash was due to the kerosene vehicle and not the DDT in the Residual Spray.

Photograph VI shows the rash on the limbs on Sunday, the 2nd September, 1945, when the condition was starting to subside.

Photograph VII shows the results of the patch tests taken on the same day, 24 hours after their application.

Cameron and Burgess (1945) found in their skin application experiments on rabbits, guinea pigs and rats that skin irritation due to kerosene was common, and showed by control experiments that this alone could kill animals. When they used emulsions, the skin at the site of application did not become inflamed.

It can be concluded that there is a danger of the kerosene vehicle in insecticide liquids causing dermatitis if it comes into prolonged close contact with the skin.

SECTION 3.

AUTHOR'S INVESTIGATION

Review of the 1944 Epidemic.

The intensive aerial bombardment of Malta which began in June, 1940, and continued until the siege was lifted in November, 1942, caused great devastation in the naval shore establishments. Owing to the progress of the North African operations, Malta rapidly became an important base for the invasion of Italy. As a result, manpower and materials were almost entirely devoted to the prosecution of the war, and a reduced standard of hygiene in these establishments had to be accepted.

In 1944, conditions were favourable for a sandfly fever epidemic among naval personnel. In the shore establishments, heaps of rubble adjoining overcrowded living accommodation had been left untouched for one summer or more, and in many instances contained obvious nitrogenous matter. The loose interstices of this rubble retained moisture and provided ideal conditions and a suitable micro-climate for the life cycle of phlebotomus, namely:-

1. Breeding grounds with high degree of humidity and nitrogenous matter.

2. Nearness to human habitations so that the female fly could get a blood meal required for fertilization of the ova.

Owing to the influx of naval personnel the overcrowding of living accommodation was considerable. Ill-ventilated, blast-damaged buildings were crammed to capacity with men, sleeping in hammocks almost touching or in 3-tier bunks. As Malta had become the main drafting centre for the Mediterranean Command, large numbers of men fresh from the

United Kingdom, and consequently highly susceptible to the disease, arrived frequently. With such favourable conditions provided for the vector and the movement of large numbers of unseasoned men through the overcrowded establishments, the fever became epidemic. Out of the total of 3,505 cases notified, the shore establishments provided 2,795 cases, or nearly 80 per cent.

Briefly, the course of the 1944 outbreak was as follows, (vide Graph 1) -

The first cases were reported about the middle of June and the case incidence in shore establishments rose rapidly from 2·4 per thousand for the week ending 9th June to 29·7 per thousand for the week ending 14th July. From mid-July there was a sharp fall in the weekly incidence-rate to around 15 per thousand until the beginning of September, when there was a second sharp rise in the number of cases, which reached its peak of 33·5 per thousand for the week ending 15th September. From then onwards the number of cases occurring rapidly became less and the epidemic ceased about the 10th of November with the onset of cooler weather.

During the 23 weeks epidemic period, 2,795 cases were reported from naval establishments in Malta or a morbidity rate of 349·5 per thousand.

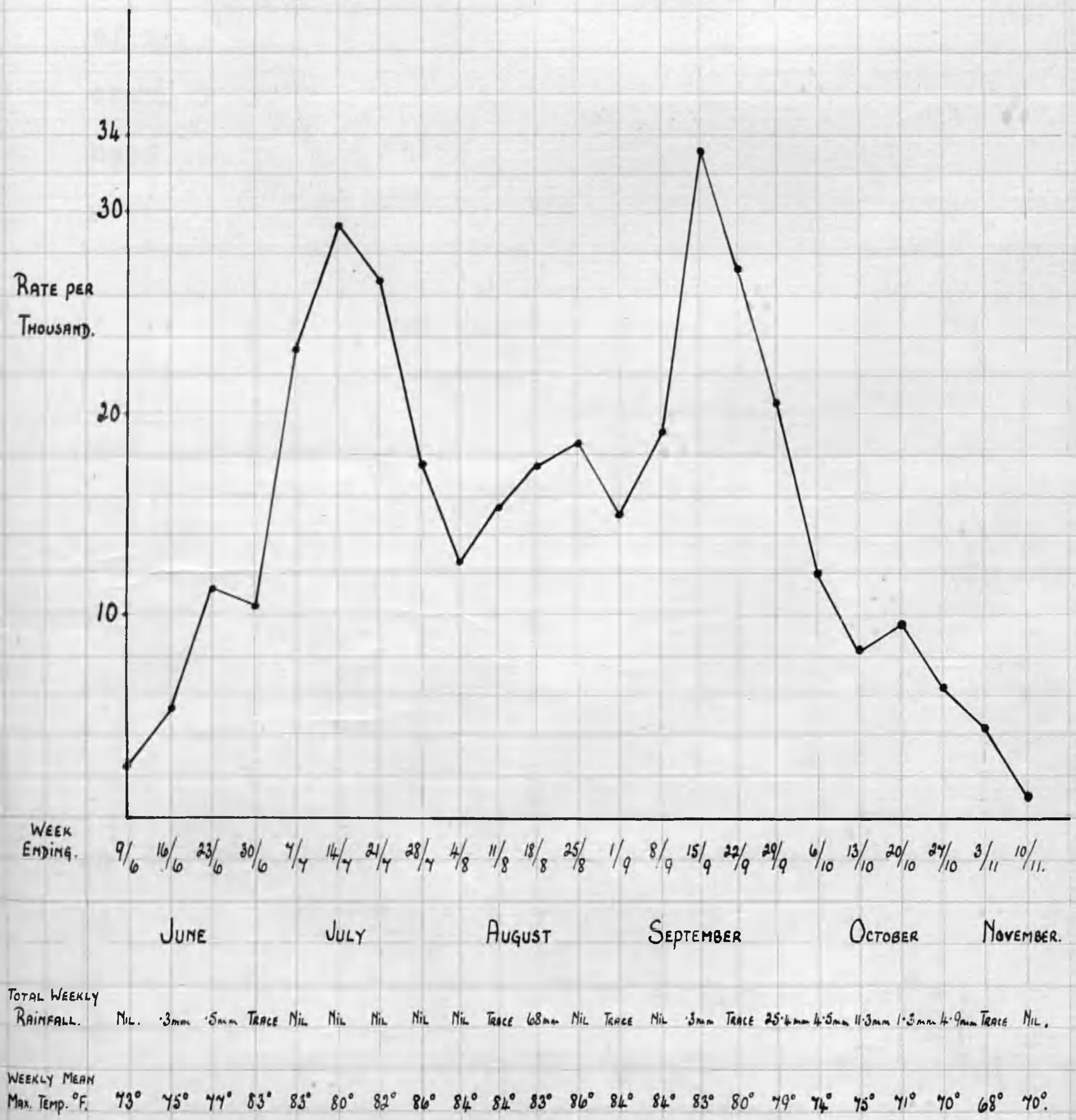
The Scheme for 1945.

The basis of the scheme was to adopt all known means for the prevention of sandfly fever and to try experimentally the effect of 5% DDT in kerosene used as a wall spray and pyrethrum and DDT anti-adult spray used as a "flit".

GRAPH 1.

SANDFLY FEVER - MALTA.
1944.

Weekly incidence-rate in Naval Shore Establishments.



i. Known Methods.

(a) Repellents.

The new insect repellent dimethyl phthalate had become available and was supplied to personnel who had to be out-of-doors at night. The results obtained with the repellent have already been described (page 98).

(b) Prevention of Overcrowding.

With the end of the War and the increased rate of release of naval personnel for demobilisation, the overcrowding in barracks could not be reduced as much as was hoped, but constant efforts were made to keep it as low as possible.

(c) Rubble Clearance.

Up to June, 1945, practically no rubble clearance had been done in naval establishments except that necessary for the working of the establishment, e.g. clearing roadways. During the summer, and especially after the Italian prisoners of war doing the rubble clearance were replaced by German prisoners of war, considerable progress was made.

(d) Sandfly Nets.

Arrangements were made for all naval personnel to be issued with sandfly nets. This measure had been adopted in 1944, but as the nets were not adapted to suit 2 and 3-tier bunks, many ratings slept without proper protection. In 1945, special nets were devised for 2 and 3-tier bunks.

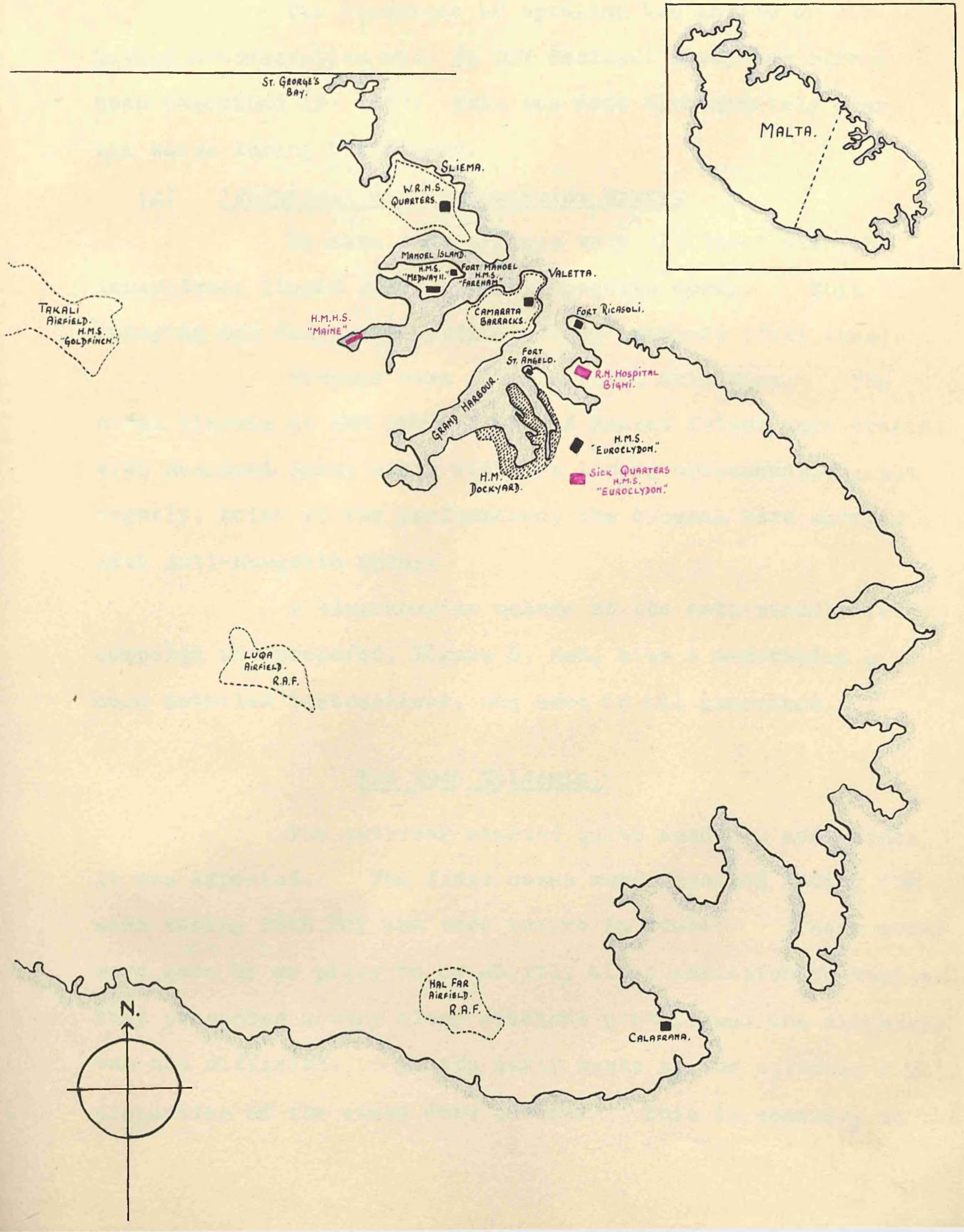
The transient ratings in HMS EUROCLYDON, who numbered approximately twelve to fourteen hundred, slept in hammocks and, in spite of numerous efforts, I was unable to devise a practical sandfly net for use with a hammock. The 'hammock mosquito net' made of sandfly netting prevented ventilation and was impracticable. Also, the fire risk from large amounts of netting festooned in a dormitory had to be borne in mind. Therefore, it was decided in the dormitories at HMS EUROCLYDON to forego the protection of nets and rely solely on the action of the 5% DDT Residual Spray.

(e) Immediate Isolation of all cases of Sandfly Fever.

In order to reduce the chance of phlebotomi acquiring the virus by biting cases of sandfly fever, arrangements were made for the isolation of all cases immediately on diagnosis in hospital accommodation which was situated at a safe distance from the large establishments (Map 2). The R.N. Hospital, standing on Bighi promontory, took the cases from the Dockyard, HM Ships in the Grand Harbour, Fort Ricasoli, Camarata Barracks, Fort St. Angelo and HMS EUROCLYDON. HM Hospital Ship MAINE, moored in Misida Creek, took the cases from the other establishments and especially the cases from the congested establishments on Manoel Island. The sick quarters in HMS EUROCLYDON had a 20-bed ward on the first floor and, as this was well away from the dormitories, it was used for a number of cases occurring in this establishment. Except in HMHS MAINE, all cases of sandfly fever were nursed under sandfly nets night and day for the first 48 hours.

MEDICAL AND NAVAL SHORE ESTABLISHMENTS IN MALTA, 1945.

MAP 2.



ii New Methods.

(f) Residual Spraying.

The technique of spraying the inside of all living accommodation with 5% DDT Residual Spray has already been described (p. 124). This was done approximately every six weeks during the summer.

(g) 'Flitting' with Insecticide Spray.

To save DDT, offices were 'flitted' with the insecticide liquid known as Anti-Mosquito Spray. This spraying was done with ordinary hand sprayers (flit guns).

Cinemas were given special attention. The naval cinemas at HMS EUROCLYDON and Manoel Island were treated with Residual Spray along with the living accommodation, but nightly, prior to the performance, the cinemas were sprayed with Anti-Mosquito Spray.

A diagrammatic scheme of the anti-sandfly fever campaign was prepared, Figure 8, and, with a memorandum giving more detailed instructions, was sent to all concerned.

The 1945 Epidemic.

The outbreak started quite suddenly and before it was expected. The first cases were reported during the week ending 18th May and were twelve in number. These cases were seen by me prior to or shortly after admission to hospital; they presented a very clear clinical picture and the diagnosis was not difficult. In the early weeks of the epidemic a fair proportion of the cases were severe. This is contrary to the

FIGURE 8.

SCHEME FOR THE PREVENTION OF SANDFLY FEVER IN MALTA. (1945).

PROTECTION

PERSONAL

Sandfly nets.
1. Used by all personnel.
2. Properly fitted.
3. In good repair.

Repellents.
Dimethyl Phthalate
Used by personnel on duty outside after sunset.

Isolation of all cases of Sandfly Fever and nursed under a Sandfly Net. To reduce numbers of infected sandflies.

ENVIRONMENTAL

Rubble contains sandfly breeding grounds. Remove as much as possible.

Hygiene Standards.
1. Cleanliness of establishment indoors and outside.
2. All refuse in lidded bins.

INFORMATION

MEDICAL OFFICER OF ESTABLISHMENT
1. Lectures to ship's company.
2. Advice to C.O.

NAVAL HEALTH OFFICER

Special problems.

Offices.
'Flit' with Anti-Mosquito Spray before occupation in morning and at sunset if occupied at night.

Living Quarters.
Spray with 5% DDT Residual Spray every six weeks.
N.B. Spray generously window surrounds, dark corners, cracks and crevices where sandflies hide.

Sick Bays, Galleys, Ablutions and Lavatories.

1. Very thorough spray with 5% DDT every month.
2. Daily 'flitting' morning and evening with Anti-Mosquito Spray.

NOTE The supply of DDT liquid insecticides is limited and care should be taken to avoid waste.

findings of Doerr and Russ (1909), who stated that the first cases in a phlebotomus fever epidemic were mild. They suggested that the virus was diminished in virulence by passage to the offspring and that virulence was regained by passage through man.

The number of cases increased rapidly, as shown in Table 14 (page 165) and Graph 2(page 153).

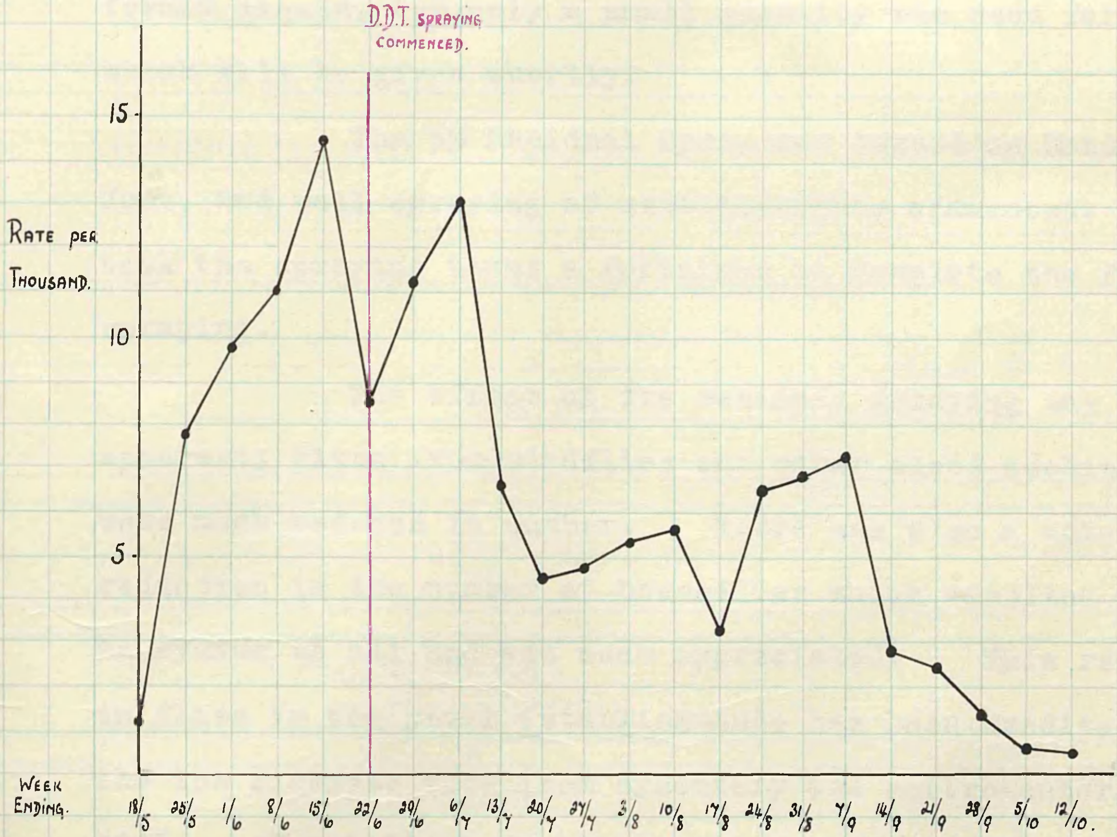
The cases were scattered among the various establishments on the island, but the spot maps showed that by far the majority of cases in these early weeks came from the submarine base on Manoel Island, HMS MEDWAY II (Graph 5 page 176).

When the first cases occurred, the only DDT available was 50 lbs. which had been supplied for experimental purposes. By the time supplies of DDT and the insecticide liquids containing DDT arrived, the epidemic had been in progress for six weeks and, in the shore establishments, 531 cases had occurred (i.e. 39% of the total cases in shore establishments. During these six weeks all the preventive measures were in operation except the spraying with 5% DDT. Commanding Officers were asked to arrange for inspections to be made to ensure that the nets were being properly used. Most individuals used their nets properly as soon as they learnt from experience that failure to do so resulted in several itching bites next day. HMS EUROCLYDON, where the ratings were sleeping in hammocks, at first remained comparatively free of sandflies and had only a relatively small number of cases. In the first weeks of June the disease greatly increased in this

GRAPH 2.

SANDFLY FEVER - MALTA.
1945.

Weekly incidence-rate in Naval Shore Establishments.



WEEK ENDING.	18/5	25/5	1/6	8/6	15/6	22/6	29/6	6/7	13/7	20/7	27/7	3/8	10/8	17/8	24/8	31/8	7/9	14/9	21/9	28/9	5/10	12/10.
	MAY		JUNE					JULY				AUGUST					SEPTEMBER				OCTOBER.	
TOTAL WEEKLY RAINFALL.	NIL	NIL	NIL	NIL	NIL	NIL	NIL	0.2mm	NIL	NIL	NIL	NIL	NIL	NIL	NIL	NIL	TRACE	NIL	TRACE	NIL	TRACE	TRACE.
WEEKLY MEAN MAX. TEMP. °F.	78°	83°	79°	81°	81°	84°	87°	83°	83°	84°	83°	89°	86°	92°	89°	85°	85°	80°	78°	76°	76°	74°.

establishment and, by this time, the unprotected men were being badly bitten.

Prior to the arrival of the Anti-Mosquito Spray, establishments were using a pyrethrum insecticide spray for 'flitting' living accommodation at sunset. This was a laborious process, and it was difficult to get it carried out efficiently in the numerous dormitories. The DDT containing Anti-Mosquito Spray was issued in lieu of the former liquid, but only a small quantity was used for reasons which will be given shortly.

The 5% Residual Spray was issued on Monday, 25th June, and wall spraying of establishments commenced. It took the spraying teams a fortnight to complete the first spraying.

The effect of the residual spraying was immediately apparent; bites from sandflies and other blood sucking insects were much reduced in number. There was also a considerable reduction in the number of houseflies which resulted in less annoyance to all and was much appreciated. This reduction in flies in the naval establishments has been credited with the low sickness rate from dysentery and gastro-enteritis in 1945. The killing of the larger insects provided ample proof of the toxic effect of DDT, and numbers of insects, dead or dying, were commonly seen on window-sills or in corners of rooms. Verandahs, where formerly sitting after dusk was well nigh impossible owing to the persistent attacks by sandflies, after the first spraying with Residual Spray, became almost clear.

During the two weeks that the first spraying was in progress, there was no diminution in the number of cases occurring in the shore establishments (Table 14 and Graph 2). Thereafter, the weekly case incidence dropped to about 5 per thousand and, apart from a slight rise in early September, gradually declined until the epidemic ended in the first weeks of October.

About mid-July it became apparent that more and more persons in the shore establishments were not using their sandfly nets, and the situation was considered with a view to deciding whether to recommend stricter enforcement of the order that all naval personnel were to sleep in sandfly nets. The following points were considered :-

(a) The summer was a very hot one and the nights were warm and calm. The overcrowded messes (dormitories) were very hot and humid. There was very little air movement in them and no fans were available. In such conditions, sleep under a sandfly net was uncomfortable, difficult and unrefreshing.

(b) At HMS EUROCLYDON, where the men were sleeping in hammocks without nets in sprayed, grossly overcrowded messes, the incidence of sandfly fever was no higher than in similar establishments (Graph 5).

(c) The WRNS, whose quarters were in an area in Sliema, which had, in previous years, been heavily infested with sandflies and where phlebotomus fever had been prevalent, were having few cases of the disease, although by mid-July large numbers of them were not using their sandfly nets. This was attributed to the fact that the WRNS slept in their own quarters every night as all the hotels and lodging-houses (except the YWCA) were out of bounds to the Women's Services for sleeping out. On the other hand, the naval ratings were frequently given overnight leave, and many of them spent the night in one or another of the many sailors' lodging-houses in Valetta or Sliema. These lodging-houses were heavily infested with sandflies, and several later proved to be foci of infection.

(d) The reports that few bites were received by persons not using their sandfly nets.

With the above indications, also, owing to the absence of malaria in Malta, and the much greater comfort which resulted from sleeping without a net, the common-sense view was taken and it was recommended that the use of the sandfly net should not be insisted upon but left to the individual. As the weeks passed and the weather grew hotter, more people abandoned their nets without any increase in the prevalence of the infection. Towards the end of August there was a slight increase in the number of cases and sandflies appeared once more. During this time many started to use their nets again, but the period of activity was short.

It is considered that the decision to make the use of the sandfly net optional was justified. Even in the hospital the patients were given the choice and it greatly added to their comfort. Of course, cases of sandfly fever were nursed under nets for the first 48 hours throughout the summer.

Finally, some amplification on the subject of lodging-houses is necessary as these premises formed, in the latter weeks of the epidemic, the places where the disease appeared to be frequently acquired.

In the island, 48 lodging-houses provided approximately 1,500 beds which were used by ratings from ships and establishments who wished to sleep 'ashore' when granted over-night leave. These premises, being civilian establishments, came under the Maltese Government Public Health Authority for sanitary control. The Naval Provost Marshall had powers to put any lodging-house out of bounds to naval personnel should the hygiene or cleanliness be reported as unsatisfactory at any time by the Naval Health Officer, but, generally speaking, the hygiene was good. The dormitories and the beds were kept clean, and fresh laundered sheets were provided for each bed every time it was occupied by a different boarder. Verminous infestation was relatively uncommon. However, in spite of their cleanliness, most of these lodging-houses were infested with sandflies. They were in the congested townships of Valetta and Sliema, often in close proximity to areas of rubble and devastation. The beds in which the ratings slept were, for the most part, in dormitories on the first, second and third floors of the buildings. None of the lodging-houses were equipped with sandfly nets. Therefore, apart from the slight protection given by natural air currents, which could not have been great in these upstairs rooms owing to the proximity of other buildings, the naval ratings slept without protection from the attacks of phlebotomi and other blood sucking insects. Yet the lodging-houses were popular as many sailors preferred their cooler and roomier dormitories as a change to the hot overcrowded mess-decks of H.M. ships and so many of the naval establishments.

In the series of 500 cases of phlebotomus fever described under Immunity (p. 85) two hundred and five, (41 per cent.) stated that they had slept ashore within the 14 days preceding the attack. This figure gives some indication of the number of naval ratings who used the lodging-houses. This did not apply to Officers and WRNS; the former could only sleep 'ashore' at the Officers' Rest Camp and the latter at the YWCA; both hostels were equipped with sandfly nets.

As the epidemic continued, it became increasingly clear that numbers of men were badly bitten with sandflies in these lodging-houses, and particular ones became undoubted foci of infection. As stocks of DDT were limited, the lodging-houses run by voluntary bodies, such as the YMCA, were sprayed, and also certain of the privately owned premises from which cases were regularly appeared to be infected.

Arrangements were discussed with the Chief Government Medical Officer for the spraying of lodging-houses with DDT in succeeding years.

There is no doubt that a considerable number of naval ratings acquired the fever whilst sleeping in lodging-houses in Valetta and Sliema. The omission of the spraying of lodging-houses from the scheme for prophylaxis of phlebotomus fever was probably the cause of the total number of cases being higher than it need have been. The lesson was learned too late for it to be fully corrected in 1945, but it was recorded and arrangements discussed for wall spraying of the lodging-houses in future years.

SECTION 4.

RESULTS.

The data available for the 1944 outbreak was the weekly incidence of reported cases in ships and the various shore establishments together with the weekly strength in the establishments during the epidemic period. In a large outbreak like that of 1944, whilst the returns or notifications of cases of phlebotomus fever probably gave a reasonably accurate picture, they made no allowance for cases in which diagnosis was altered.

Notifications of any infectious disease do not provide accurate morbidity statistics unless corrected by the hospital diagnosis: this was done in 1945.

As almost all cases of sandfly fever were admitted to the R.N. Hospital, HMHS MAINE or R.N. Sick Quarters HMS EUROCLYDON, the weekly returns from the establishments were checked against the hospital returns and allowance made for instances of altered diagnosis. Most of the Medical Officers in the shore establishments had been in Malta during the previous epidemic season and were familiar with the clinical syndrome, so the number of cases of altered diagnosis was small.

The Supply Officers of each establishment kindly worked out a weekly average strength for me from their records of the numbers victualled daily. The range of the total weekly strengths was small, the lowest being 7,886 and the highest 12,025, the majority being around 10,000. The arithmetic mean of the weekly populations for the epidemic period was 9,988.

For convenience, the week was taken to end at midnight each Friday. This allowed the returns to be collected over the week-end and a weekly summary of the progress of the epidemic promulgated each Monday.

As the experiment was essentially concerned with the prevention of phlebotomus fever in naval shore establishments, the cases occurring in HM ships at Malta are not included in the detailed analysis of the results. Table 12 shows numbers of cases from HM ships and shore establishments in 1944 and 1945.

Table 12.

Numbers of Cases from HM Ships and Shore Establishments in 1944 and 1945

Year	Total number of cases.	HM Ships Number of Cases	Shore establishments	
			Number of cases.	Percentage of total.
1944	3,505	710	2,795	79·7
1945	1,457	92	1,365	93·7

This table indicates that the infection in both years mainly affected the naval personnel living ashore.

Graph 1 and Table 13 show the weekly incidence of cases in the 1944 epidemic. The epidemic curve clearly illustrates the points first recorded by Whittingham and Rook (1923[1] and 1923[2]) regarding the course of an epidemic of phlebotomus fever in Malta, namely that :-

(a) Two waves of the disease occur annually, each lasting three to four weeks.

(b) The first wave occurs at the beginning of the hot weather

Table 13

Weekly Incidence of Sandfly Fever
in Shore Establishments in Malta.
1944

Average Strength of Shore Establishments - 8,010.

Week ending	Incidence-rate per thousand
Jun. 9	2.4
" 16	5·5
" 23	11·5
" 30	10·8
Jul. 7	23·8
" 14	29·7
" 21	26·7
" 28	17·9
Aug. 4	12·7
" 11	15·8
" 18	17·9
" 25	18·8
Sep. 1	15·3
" 8	19·2
" 15	33·5
" 22	27·1
" 29	20·6
Oct. 6	12·0
" 13	8·5
" 20	9·7
" 27	6·3
Nov. 3	4·2
" 10	1·4

Incidence-rate per thousand for Epidemic Period = 349·36.

and the second in the autumn, separated by a two months lull.

Whittingham (1938) claimed that the first wave was caused by phlebotomi hatched from larvae which had survived the winter and that the autumn wave was due to the second brood of insects. He based his view on the fact that the interval between the epidemic waves was about eight weeks, the approximate time required for the phlebotomi to complete the life cycle.

This graph is the typical epidemic curve for sandfly fever in the Mediterranean littoral (Milne, 1945, and others).

Table 14 and Graph 2 indicate the course of the epidemic in 1945. During the first six weeks of the epidemic period, that is up to the 22nd June, 1945, when the DDT-containing Residual Spray became available, 531 cases occurred in the shore establishments or 38.9 per cent. of the number of cases in shore establishments during the epidemic. The graph shows how the incidence rate rose during the two weeks that spraying was in progress, then with the disappearance of sandflies from the sprayed naval premises, the incidence rate fell sharply, and, for the rest of the epidemic, never exceeded 7.2 per thousand.

There was a slight rise in the incidence or attack-rate of the fever between the 17th August and the 7th September, 1945. During this period sandflies became noticeable again. In the weeks prior to this, prolonged searches had been made in the sprayed wards of the R.N. Hospital, but no phlebotomi could be found. At this time three phlebotomi were caught, of which two died within an hour

Table 14.

Sandfly Fever Epidemic - 1945

Weekly Incidence of Cases.

Week ending	Total Naval cases	Cases Shore Est' ments.	Rate per 1000	Cases HM Ships	Cases WRNS	Army Rate per 1000	RAF Rate per 1000
May 18	12	12	1·2	-	-	-	0·4
" 25	90	79	7·9	11	7	0·1	2·2
Jun 1	103	99	9·9	4	2	0·1	2·8
" 8	110	110	11·0	-	3	1·6	3·6
" 15	145	145	14·5	-	2	1·8	3·0
" 22	92	86	8·6	6	3	2·4	3·4
" 29	119	111	11·1	8	3	3·1	4·5
Jul 6	136	131	13·1	5	2	3·3	4·3
" 13	82	67	6·7	15	-	1·7	2·4
" 20	60	46	4·6	14	2	1·2	1·0
" 27	53	48	4·8	5	3	2·5	2·8
Aug 3	54	54	5·4	-	2	2·2	2·9
" 10	60	56	5·6	4	2	2·0	2·9
" 17	37	33	3·3	4	1	0·9	2·3
" 24	65	65	6·5	-	3	2·5	3·2
" 31	72	68	6·8	4	4	2·0	4·0
Sept 7	74	72	7·2	2	3	1·5	3·8
" 14	32	29	2·9	3	3	1·15	2·3
" 21	26	24	2·4	2	2	0·05	1·1
" 28	20	15	1·5	5	-	-	1·1
Oct 5	8	8	0·8	-	-	0·03	0·9
" 12	7	7	0·7	-	-	-	0·3
TOTALS	1457	1365		92	47		

Average Weekly Strength of Shore Establishments = 9,988.

Incidence-rate per thousand for Shore Establishments = 136·5.

but one was induced to take a blood feed and remained alive in captivity for several hours; unfortunately it escaped.

It is my submission that this slight increase during late August and early September was the much reduced second wave of the epidemic and that this reduction was largely due to the spraying of the insides of living rooms in the naval shore establishments with 5% DDT Residual Spray.

The other preventive measures - nets, isolation of cases and 'flitting' of accommodation with an insecticide spray, were all in action from the beginning of the outbreak, but these seemed of little avail in checking the rapid spread of the disease. No doubt these measures played a part in reducing the number of cases in the first weeks.

The sandfly nets must have given considerable protection. During May and June patients seen with numerous insect bites on their bodies frequently stated that they had slept without using the sandfly nets or had thrown them off during the night due to the stuffiness caused. Many new-comers who tried sleeping without nets or without adjusting them properly, were badly bitten as a result, and several, in my acquaintance, developed phlebotomus fever.

'Flitting' with an insecticide liquid was going on to a limited extent, but, due to the labour involved in spraying large mess decks, this was never very thoroughly carried out. After the effectiveness of the wall spraying was appreciated, practically no 'flitting' was done.

The value of prompt isolation of cases away from the overcrowded establishments is obvious, but the extent to which the measure was effective in 1945 cannot be estimated. It is worth recording that, in 1944, the Submarine Base HMS MEDWAY II nursed most of the cases of phlebotomus fever which occurred in the establishment in a gloomy dormitory which was converted into a temporary sandfly fever ward with 80 beds. This ward was in the midst of the ratings' living accommodation. When it was mooted in 1945 to use this dormitory again, the suggestion was resisted on the grounds that it provided a focus of infection in the midst of an overcrowded barracks. It is my opinion that this dormitory was probably the main source of the infection of the sandflies in HMS MEDWAY II, and also allowed a heavy infection of the breeding grounds in this area to occur. For this reason HMS MEDWAY II was a hotbed of the disease in 1944 and again in 1945 (Graph 5).

In Graph 3, the incidence rates for corresponding weeks of 1944 and 1945 are plotted. The total weekly rainfall and the weekly mean maximum temperatures are also given.

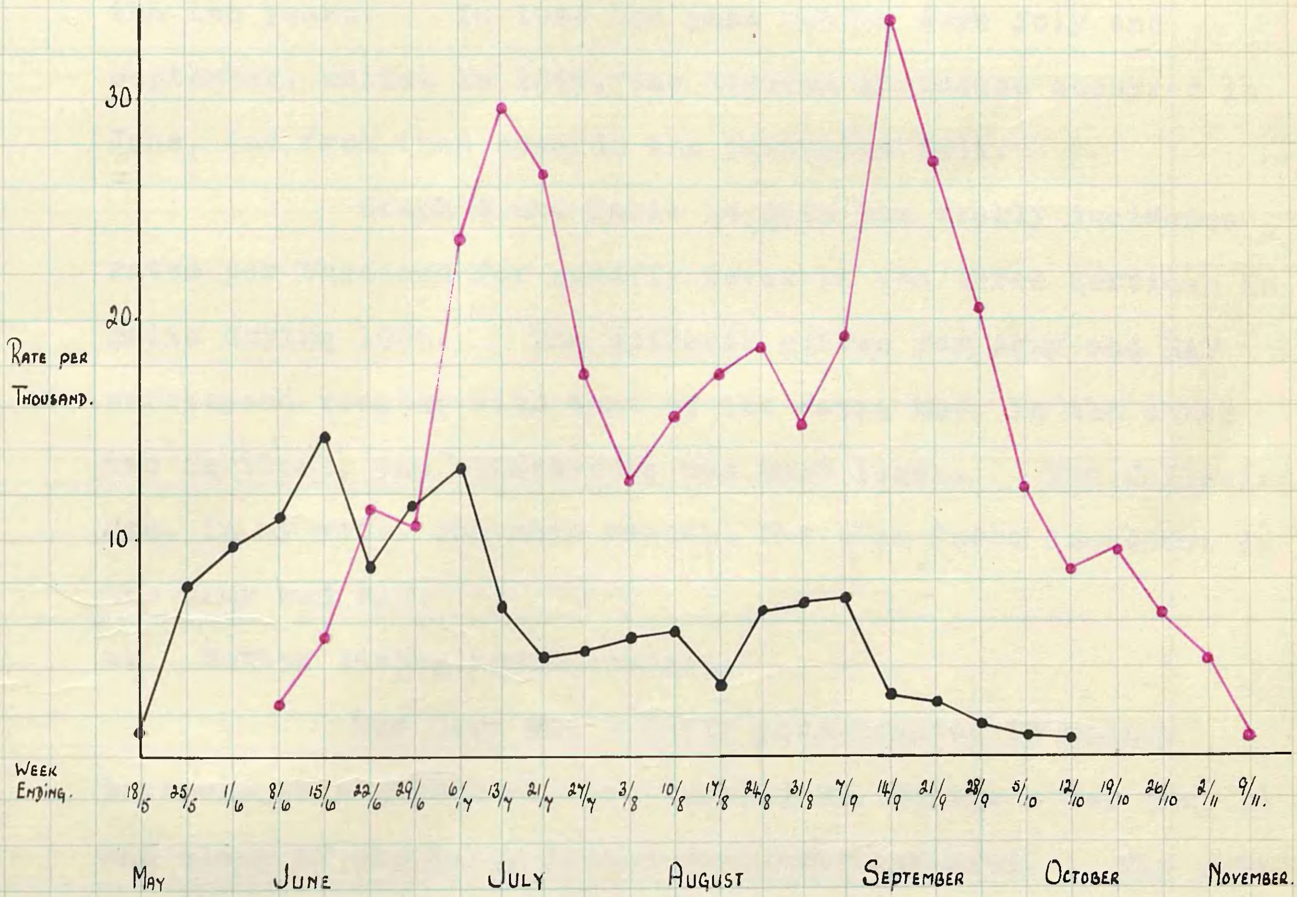
The graphs illustrate the flattening of the second wave of the disease and the much lower incidence in 1945.

The meteorological data shows that the summer of 1945 was hotter and drier than the summer of 1944. Higher temperatures accelerate the life-cycle of phlebotomus (Whittingham and Rook, 1923[2]; Young, Richmond and Brendish, 1926). Sufficient moisture is apparently always available to maintain the humid micro-climate required in the breeding grounds by evaporation from the soil and the heavy dew which falls in places with sub-tropical maritime climates like Malta (Whittingham 1938). It is generally believed that hot, dry

GRAPH 3.

SANDFLY FEVER - MALTA.
1944 and 1945.

Weekly incidence-rates in Naval Shore Establishments for corresponding weeks.



Week ending	18/5	25/5	1/6	8/6	15/6	22/6	29/6	6/7	13/7	21/7	27/7	3/8	10/8	17/8	24/8	31/8	7/9	14/9	21/9	28/9	5/10	12/10	19/10	26/10	2/11	9/11
1944 Total Weekly Rainfall.				Nil	·3mm	·5mm	Trace	Nil	Nil	Nil	Nil	Nil	Trace	68mm	Nil	Trace	Nil	·3mm	Trace	25·4mm	4·5mm	11·3mm	1·3mm	4·9mm	Trace	Nil.
Weekly Mean Max. Temp. °F.				73°	75°	77°	83°	83°	80°	82°	86°	84°	84°	83°	86°	84°	84°	83°	80°	79°	74°	75°	71°	70°	68°	70°.
1945. Total Weekly Rainfall.	Nil	Nil	Nil	Nil	Nil	Nil	Nil	0·2mm	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Trace	Nil	Trace	Nil	Trace	Trace.				
Weekly Mean Max. Temp. °F.	78°	88°	79°	81°	81°	84°	87°	83°	83°	87°	88°	89°	86°	92°	89°	85°	85°	80°	78°	76°	76°	74°.				

summers are most favourable to the appearance of large numbers of sandflies.

The higher temperatures in May, 1945, satisfied the earth temperature requirement of over 60° F. and allowed the insects which had passed the winter in the fourth larval stage to complete their life cycle; this, in my view, accounted for the earlier appearance of cases in 1945.

Table 15 gives the monthly incidence of cases in the two years. In 1944 the peak months were July and September, whilst in 1945, the highest incidence occurred in June, and from then onwards the incidence fell.

Graph 4 and Table 14 give the weekly incidence-rates per thousand for sandfly fever in the three Services in Malta during 1945. The epidemic curves for Army and RAF correspond roughly with that of the Navy, but, in the other two Services, the attack-rate was much lower. The following are, in my view, the main reasons for this lower incidence in the Army and RAF.

a. Better living accommodation.

The Army was largely accommodated in modern barracks on a promontory overlooking St. George's Bay (Map 2) and clear of the badly bombed Grand Harbour area. The rubble from bomb damage had almost entirely been cleared up by 1945. The RAF, as a result of the reduction in numbers of personnel on the Island, was well housed, mainly at the airfields of LUQA and HAL FAR. Priority had been given to putting the badly bombed airfields in working order, and this included rubble clearance and provision of new living accommodation

Table 15.

Monthly Incidence of Cases in 1944 and 1945.

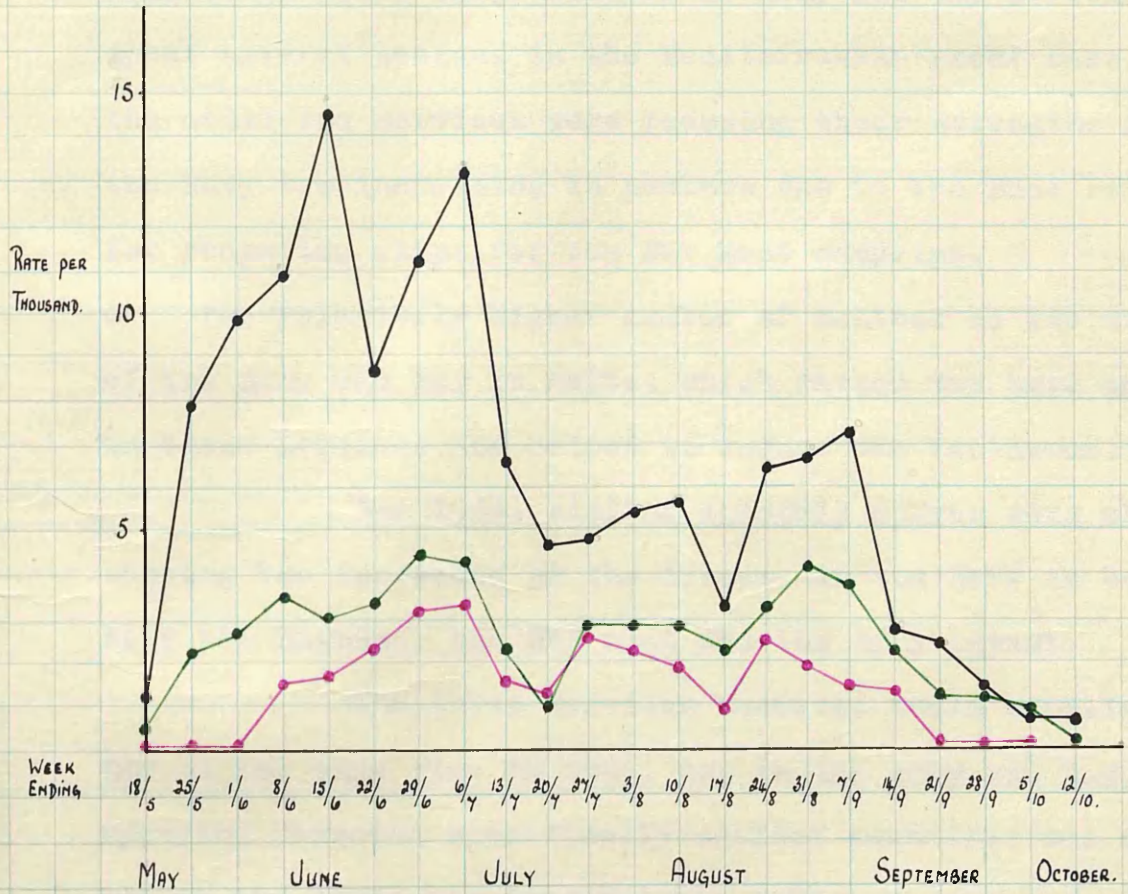
MONTH	1944		1945	
	Number of Cases	Incidence-rate per thousand	Number of Cases	Incidence-rate per thousand
May	-	-	91	9.1
June	254	31.8	551	55.1
July	794	99.2	292	29.2
August	674	80.9	276	27.6
September	805	100.7	140	14.0
October	295	36.9	15	1.5
TOTAL	2795	-	1365	

GRAPH 4.

SANDFLY FEVER - MALTA.
1945.

Weekly incidence-rates in the

Royal Navy
Army
Royal Air Force



where required. Also, as the airfields were in the centre of the island and somewhat exposed, sandflies were not so troublesome. At the naval airfield at Takali (Map 2) the incidence of sandfly fever was low (Graph 5) in spite of the overcrowded living conditions.

b. More seasoned personnel.

In the Army and the RAF, the overseas tour of service was four to five years, whilst in the Navy the overseas commission lasted approximately two and a half years. As a result, in 1945, large numbers of Army and RAF personnel had spent several seasons in the Mediterranean area: also, whilst the other two Services were reducing their strengths in Malta, the Navy was increasing in numbers due to the Base being used for preparing ships for the Far East campaign.

c. The relatively higher number of Maltese on the strengths of the Army and RAF in Malta, which raised the herd immunity in those Services and helped to reduce the incidence.

For 1944, similar epidemic curves were obtained, showing the incidence of the disease in the Navy to be considerably the highest, the RAF next and the Army lowest.

The three Services received their supplies of DDT at the same time in 1945, but in the Army and RAF, no wall spraying directed specifically against sandflies was carried out as the other Services had not suffered so badly as the Navy in the previous year. Table 16 shows that the incidence rate ratio between the Navy and the other Services in the second peak of the epidemic was appreciably reduced and, as no other known circumstances changed, this tends to suggest

Table 16.

1945

Average Incidence-rates of the three Services for the two 5-weekly peak periods and ratios of the incidence-rates compared with Army.

	First Peak Period 15 June to 13 July.		Second Peak Period 17 Aug. to 14 Sep.	
	Average Incidence-rate per thousand for period.	Ratio to Army incidence-rate.	Average incidence-rate per thousand for period	Ratio to Army incidence-rate.
ARMY	2.4	1.0	1.6	1.0
RAF	3.5	1.5	3.1	1.9
NAVY	10.8	4.5	5.3	3.3

that the DDT wall spraying campaign in Naval shore establishments was responsible for the reduction.

The incidence of the infection in the individual shore establishments is given in Table 17 and Graph 5. HMS MEDWAY II, the Submarine Base, which also served as a transit camp, suffered most. This establishment was in the buildings which were formerly the Lazaretto and Quarantine Station of the Knights of Malta. The old wards in the hospital or lazaretto part of the premises were used as living accommodation for officers and some of the ratings, whilst most of the ratings lived on mess decks in the former merchandise storehouses of the Quarantine Station, where, in bygone days, all merchandise was kept for a fixed period before being allowed to pass into the possession of the inhabitants of Malta. These storehouses (locally known as cavaliers) were of considerable length, and had arched ceilings about 50 feet high. The difficulties of spraying such compartments are obvious.

Camarata Barracks, an establishment which was used for communications, ratings and transient ratings, also had large dormitories with high ceilings and was situated in Valetta close to some of the worst bomb damage on the island.

HMS EUROCLYDON fared better than was expected, which, in my opinion, was mainly due to the thorough spraying of the mess decks with the Residual Spray. In this establishment, the ceilings in the mess decks were 12 feet high - much lower than normal for Maltese buildings - so the walls and the adjoining parts of the ceilings could be sprayed without

Table 17.

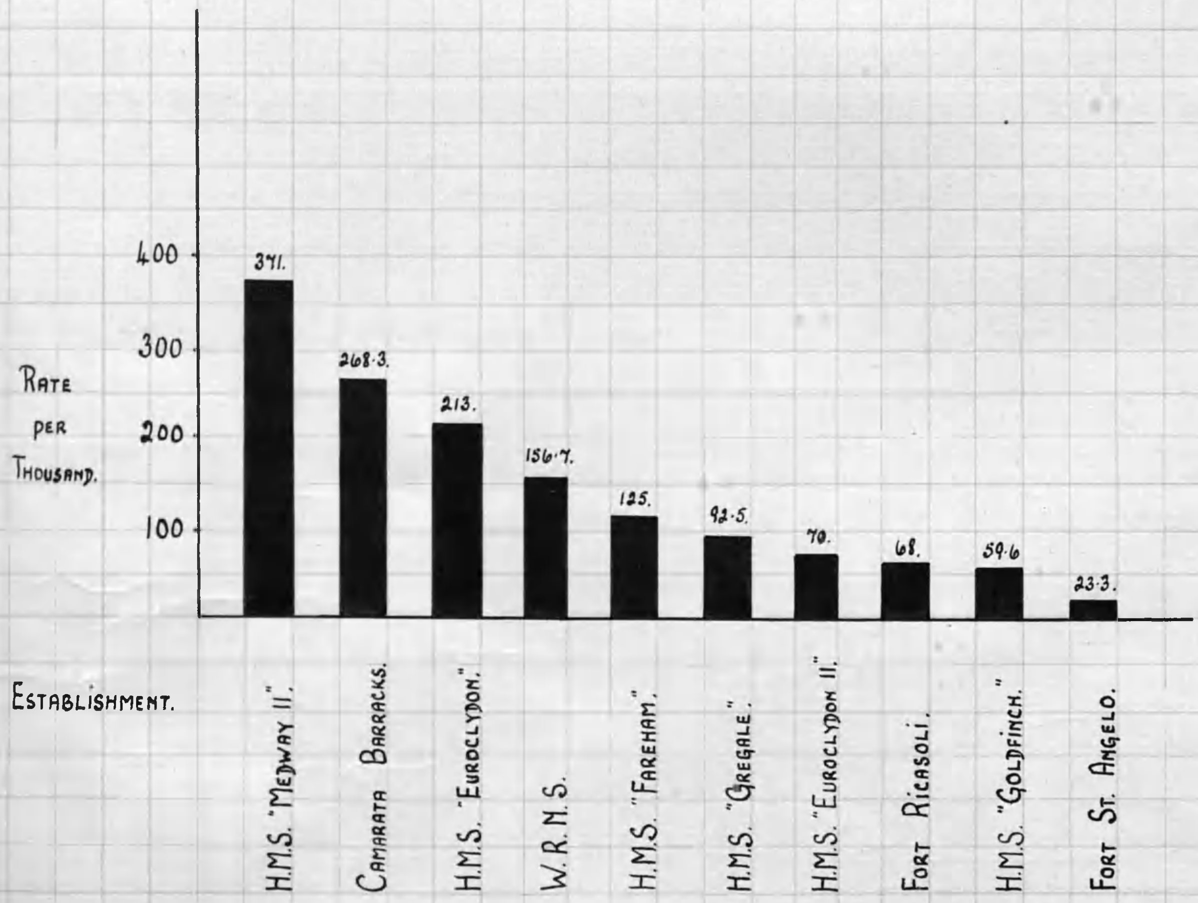
Incidence-rate per thousand for each shore establishment in the epidemic area.

Establishment	Incidence-rate per thousand.
HMS MEDWAY II	371·0
CAMARATA	268·3
HMS EUROCLYDON	213·0
WRNS	156·7
HMS FAREHAM	125·0
HMS GREGALE	92·5
HMS EUROCLYDON II	70·0
FORT RICASALI	68·0
HMS GOLDFINCH	59·6
FORT ST. ANGELO	23·3

GRAPH 5.

SANDFLY FEVER - MALTA.
1945.

Incidence-rate per thousand in each Shore Establishment during the Epidemic Period.



difficulty.

The very low figure for FORT ST. ANGELO was due to the large number of Maltese ratings borne. This establishment has served for a number of years as the depot for Maltese naval personnel.

SECTION 5.

SUMMARY AND CONCLUSIONS.

SUMMARY.

Phlebotomus fever is a disease of Military importance; it can incapacitate large numbers of troops for 7 to 14 days, often when their services may be needed most.

The existing knowledge of the disease has been reviewed. Particular attention has been paid to the life history and bionomics of the vector, Phlebotomus papatasii, as this is the foundation on which the scheme of prophylaxis has been built. Russian research, which strongly supports the theory of hereditary transmission of the virus from the adult fly to the egg, has been discussed. An account has been given of extensive work done in India and Russia on the cultivation of the virus and the preparation of a protective vaccine against phlebotomus fever. Prior to the advent of DDT, individual protection by means of a vaccine offered the most hopeful means of control of this fever.

Clinical and epidemiological experiences in the 1945 outbreak in Malta have been reported, together with observations on the clinical course of the disease in a series of 153 cases treated in the R.N. Hospital.

In a series of 500 cases in 1945, second attacks occurred in 7·8 per cent., and third attacks in 0·8 per cent. of cases. Persons who had suffered from the disease in previous years were also attacked.

Tests with dimethyl phthalate gave favourable impressions of the use of this substance as a repellent to

Phlebotomus papatasii and as a useful anti-sandfly measure for persons like sentries whose duties caused them to have to stand about out-of-doors during the hours of darkness.

The recommended preventive measures against phlebotomus fever have been discussed. Control of this disease, especially under active service conditions, has always been notoriously difficult. The recognised preventive measures in so far as they could be employed failed to check the epidemic in 1944. DDT was used as the main prevemtive measure in 1945 with success. The method employed was wall spraying with a solution of 5 per cent. DDT in kerosene in a dosage of 56 mgm DDT per square foot, at six weekly intervals. This gave almost complete control of sandflies indoors, and, for the latter part of the epidemic, other means of protection, such as the use of sandfly nets, were not insisted upon. After spraying was started there was a reduction in the number of cases and the second peak of the disease was considerably modified. The chief advantages of the DDT spray were its cheapness, economy of labour and its suitability for dealing with temporary quarters.

CONCLUSIONS.

1. Epidemic tendency.

In areas where phlebotomus fever is endemic, the chief factors which govern the tendency for the disease to become epidemic are:-

(a) Variation in the environmental and meteorological conditions affecting the numbers of infected P. papatasii which reach maturity.

(b) The numbers of susceptible persons in the area.

2. Immunity.

One attack of phlebotomus fever gives immunity to most individuals for the epidemic period, but the immunity is not lasting and attacks can occur in subsequent years. Second attacks and rarely third attacks may occur in one person during the same epidemic period.

3. Dimethyl Pthalate.

Dimethyl phthalate appears to be an effective repellent to P. papatasii, and should prove useful for the protection of persons exposed to the attacks of sandflies.

4. Impregnated mosquito netting.

Mosquito netting impregnated with DDT appears to be an efficient sandfly barrier and could be used to replace the close mesh sandfly net.

5. Toxicity of DDT.

There is little danger of toxic effects from DDT when used as a 5 per cent. spray in kerosene, and with reasonable care, protective clothing need not be worn. Irritation of the skin from the kerosene vehicle can occur.

6. Wall spraying.

Spraying the inside of living accommodation with 5 per cent. DDT in kerosene gives such a high degree of control of sandflies that other anti-sandfly measures may be relaxed. In regions where malaria and sandfly fever are both endemic, it is suggested that, in sprayed sleeping quarters, a mosquito net impregnated with DDT will give complete protection.

DDT should not become the sole means of attack against phlebotomus. A high standard of hygiene and the elimination of sandfly breeding grounds in barracks remains as the most important long term preventive measure.

All sleeping accommodation, including hostels and lodging-houses, must be included in the wall spraying programme for the effective control of phlebotomus fever.

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