Section of Epidemiology and State Medicine

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Observations on an Epidemic of Cerebrospinal Meningitis in Cyprus and the Record of a Prophylactic Experiment

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ABSTRACT.—After a lapse of twenty-five years cerebrospinal meningitis appeared again in epidemic form during 1936-37.

A prophylactic inoculation experiment was undertaken during the autumn of 1937, a few months before the second epidemic season was due to begin.

Season 1936-37—836 cases—284 deaths.

Season 1937-38 (after inoculation)—298 cases—81 deaths.

Season 1938-39—122 cases—51 deaths (to end of May, 1939).

During the second season conditions were suitable for the continuance of the epidemic. We do not think that we obtained a false result by inoculating on a waning epidemic. Our results are inconclusive because owing to the sharp decline in the morbidity neither control nor inoculated groups were fully at risk. But our results are good enough to recommend a further trial of prophylaxis in future epidemics. The percentage of the population inoculated is an important factor. The aim should be 100%.

The experiment should aim at controlling not only the meningococcal carrier rate but also the general catarrh rate. We suggest that the rapid passage of the meningoccocus in association with an epidemic of nasopharyngeal catarrh raises the virulence of the meningococcus.

As the opportunity of a second experience in the prevention of cerebrospinal meningitis by prophylactic inoculation seldom occurs to an individual, we take this chance of making recommendations for guiding future experiments.

RÉSUMÉ.—Après un intervalle de 25 ans la méningite cérébrospinale a reparu en Chypre en forme d'épidémie en 1936-37.

Un essai d'inoculation prophylactique a été fait en automne 1937, quelques mois avant la date attendue du commencement de la seconde saison de l'épidémie.

Saison 1936-37—836 cas—284 morts.

Saison 1937-38 (après inoculation)—298 cas—81 morts.

Saison 1938-39 —122 cas—51 morts (jusqu'à la fin de mai, 1939).

Pendant la deuxième saison les conditions étaient favorables pour l'épidémie. Nous ne croyons pas avoir obtenu de faun résultats en inoculant pendant une épidémie décroissante. Nos résultats ne sont pas décisifs parce que, en vue de la diminution brusque de la morbidité, ni le groupe vacciné ni les contrôles étaient exposés à tout le risque d'infection. Toutefois les résultats sont assez bons pour justifier la prophylaxie pendant des épidémies futures.

La proportion de la population soumise à la vaccination est importante; le but doit être 100%.

L'experience doit chercher à contrôler non seulement la proportion de porteurs de méningocoques, mais aussi la proportion de catarrhes généraux.

Nous suggérons que le passage rapide des méningocoques associé à une épidémie de catarrhe naso-pharyngien augmente la virulence des méningocoques.

Comme un individu n'a que rarement l'opportunité de prévenir une seconde épidémie de méningite cérébrospinale par l'inoculation prophylactique, nous profitons de cette occasion pour faire quelques recommendations pour guider les expériences futures.

ZUSAMMENFASSUNG.—Nach einer Zwischenzeit von 25 Jahren trat die Meningitis cerebrospinalis in Cypern im Jahre 1936-37 wieder als Epidemie auf.

Ein Versuch mit prophylaktischer Impfung wurde im Herbst 1937 unternommen, einige Monate vor dem erwarteten Beginn der zweiten Welle der Epidemie.

Saison 1936-37—836 Fälle—284 Todesfälle.

Saison 1937-38 (nach Impfung)—298 Fälle—81 Todesfälle.

Saison 1938-39—122 Fälle—51 Todesfälle (bis Ende Mai).

Während dem zweiten Saison waren die Verhältnisse für das Fortbestehen der Epidemie günstig. Wir glauben nicht dass wir durch Impfung während einer abklingenden Epidemie zu falschen Ergebnissen gekommen sind. Die Ergebnisse sind wegen der raschen Abnahme der Morbidität nicht entscheidend, da weder die Geimpften noch die Kontrollgruppe dem vollen Risiko ausgesetzt waren. Immerhin sind sie so gut dass prophylaktische Impfung bei zukünftigen Epidemien zu empfehlen ist.

Der Prozentsatz der geimpften Bevölkerung ist ein wichtiger Faktor. Das Ziel müsste 100% sein.

Der Versuch sollte auf die Kontrolle nicht nur des Meningokokkenträger Verhältnisses, sondern auch des gewöhnlichen Katarrh Verhältnisses zielen.

Wir weisen darauf hin, dass die rasche Passage von Meningokokken während einer Epidemie von Nasen-Rachen Katarrh die Virulenz der Meningokokken steigert.

Da nur sehr wenig Beobachter Gelegenheit haben einen zweiten Versuch der prophylaktischen Impfung gegen Meningitis cerebro-spinalis zu unternehmen, benutzen Verff. diese Gelegenheit um Richtlinien zur Durchführung weiterer Untersuchungen zu geben.

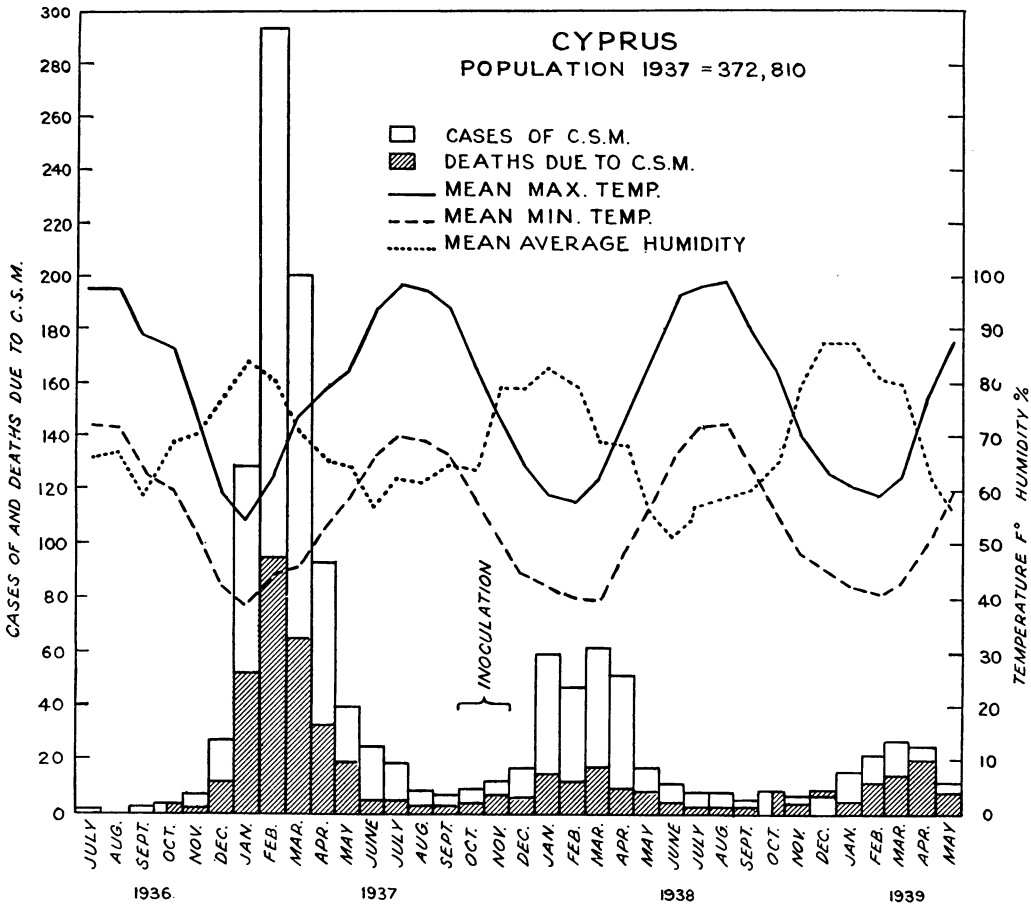
CEREBROSPINAL MENINGITIS IN CYPRUS

THE history of cerebrospinal meningitis in Cyprus has recently been reviewed by Neff and Markides (1937). From this survey it appears that the first recorded outbreak of the disease occurred in the winter of 1887 to 1888, when over 400 cases were reported. At this time all health records seem to have been very incomplete, and it is probable that these figures by no means represent the total number of cases that occurred. From 1888 to 1908 only an occasional case of this disease is recorded, but in the spring of that year 140 cases with 96 deaths are recorded. In the following winter there were 1,153 cases with 600 deaths; in the next season 1,080 cases with 546 deaths. In the fourth season 84 cases are mentioned but there is no record of the number of deaths. Details of these epidemics are scanty, but in the 1908–09 wave it is stated that 55% of cases were under 20 years of age and 30% in the 10–20 age-group. The epidemic waves occurred in the winter, with the maximum incidence in February and March.

Since 1910 cases of cerebrospinal meningitis have occurred sporadically with an occasional slight increase in incidence. Thus, there were 25 cases reported in 1913, 48 in 1918, and 27 in 1921. 1935 was the only year since 1908 in which no cases were reported; but in July and September 1936 isolated cases were reported from different districts. The September case was followed within a week by a case in a miner employed by the Cyprus Mines Corporation who had come from the same district. At the mines conditions commonly thought to predispose to an epidemic of cerebrospinal meningitis were all present, viz. overcrowding, fatigue, dust, excessive alcohol consumption, prevalence of nasopharyngeal catarrhs, and a constant supply of new recruits.

From the mines the disease spread to the neighbouring villages so that in December 1936, 26 cases were reported. The incidence reached its peak in February 1937 when 288 cases were notified. As the weather became warmer, the epidemic gradually subsided so that only seven cases were notified in August, and six in September. The number of cases and deaths and the meteorological conditions observed in Cyprus, are correlated in Graph I; that the greatest number of cases occurs when the maximum temperature in degrees Fahrenheit has fallen to below the relative

humidity at 2 p.m. expressed as a percentage; and that the incidence of the disease lags roughly one month behind the changes in the meteorological observations. The cold, wet weather, not only accentuates the overcrowding, but also increases nasopharyngeal catarrh. During the winter of 1936–37 there was a widespread epidemic of mild influenza, associated with considerable catarrhal symptoms but without many serious complications. The influence of climatic conditions in Cyprus therefore appears to be the direct opposite to that observed



GRAPH I.—Progress of cerebrospinal meningitis in Cyprus (1936-39) correlated with the meteorological conditions and the inoculation experiment.

in the Sudan, where the dry, dusty weather is associated with catarrh and cerebrospinal meningitis.

The distribution of cases during the twelve months from October 1, 1936, is shown in Maps 1 and 3 (*see* pp. 1569 and 1571), where it can be seen that the disease is concentrated near the main roads leading from the mines. The coastal region immediately west of the mining area (Tyllaria area) was more particularly affected. It should be noted that this area is one of the worst malarious regions in the island; and on the average the houses are smaller and more crowded than in other parts of Cyprus. We have gained the impression that malaria has had some influence on the distribution of cerebrospinal meningitis, though it is difficult to obtain any

direct evidence. Contact with the mines is unquestionably the most important factor, but it seems that in the case of places with equal contact, those villages with a high malaria incidence had a higher incidence of cerebrospinal meningitis compared with those with little or no malaria. Paphos district and the Tyllaria area have the highest spleen rates and also the greatest incidence of cerebrospinal meningitis. Individual villages that had particularly high incidence were nearly always malarious.

70% of the cases occurred in those under 30 years of age, 41% in those under 10. The disease was less severe clinically than that usually experienced in Great Britain.

Following the first wave, and before the expected second wave of the epidemic, it was decided to try the use of a prophylactic vaccine on a large scale.

Previous Prophylactic Vaccination

The first attempt at prophylactic vaccination against cerebrospinal meningitis was done by Davis (1907) who had to give up this work because his large doses caused severe reactions—in some cases amounting to meningism. Sophian and Black (1912), using doses of 500, 1,000 and 2,000 million organisms at weekly intervals, got better results, and established that their vaccine gave an immune response comparable with that found in convalescents. Kolmer and Rule (1938) working with guinea-pigs, rabbits and monkeys, showed that active vaccination protected these animals against infecting doses of meningococci which were capable of killing or (in the case of monkeys) causing the disease, in all their control animals.

Greenwood (1916) and Gates (1918) reported in favour of prophylactic inoculation but gave no control results. Bruynoghe and Walwarrens (1930), Le Bourdelles and Sedallian (1930), Saleun and Ceccaldi (1936), Yacob (1935), Russell (1936), Zrūnek and Feierabend (1931), Sorel (1937), all reported a lower case incidence among their inoculated than among the control groups. The above worked during epidemic periods, and yet all considered that that their inoculation had had a favourable effect on the course of the epidemic. Zrūnek and Feierabend also inoculated out of epidemic times certain garrisons which had a bad history for cerebrospinal meningitis during previous seasons. Although the incidence of the disease was as great among the inoculated as among the control non-inoculated, they concluded that the garrisons where at least 50% of the men had been inoculated fared very much better than did garrisons where no inoculation had taken place. This change for the good in the inoculated garrisons occurred in spite of an alteration of personnel and the arrival of many new recruits. The benefits cannot therefore be attributed to any increased immunity of the population due to salting. For example, in 1926 there were 31 cases in the selected garrisons whereas after inoculation in 1927 there were only 10. On the other hand in a similar group of garrisons where no inoculations had taken place the ratio of cases in the same two years was as 21 to 16, showing that the incidence of the disease was greatly reduced in the inoculated garrisons but had persisted in the others. These numbers are small and they can only be considered as a pointer of the way prophylactic inoculation works in this disease.

Riding and Corkill (1932) report a failure for prophylactic inoculation. They compared the number of cases occurring in Group A (meningococcal vaccine) with a similar Group B (TAB vaccine). Both groups had an almost equal incidence, but the control group should have been all the uninoculated in the district. They inoculated in Deims at the peak of the epidemic, and they allowed only one day for the immunity from the vaccine to develop. They do not say how many cases occurred in this place within the next four days, which most immunologists would have considered the shortest period in which immune bodies could have developed after vaccination. In Khartoum city, where they inoculated before the peak of the epidemic, their results were much better, viz. :

Inoculated Group A (meningococcal vaccine)	2,584	No cases
Inoculated Group B (TAB vaccine) ..	2,807	5 cases
Uninoculated (rest of population) ..	4,809	22 cases

Read this way, their results are in favour of meningococcal prophylactic inoculation in epidemic cerebrospinal meningitis.

There are thus two ways of reading results: (1) Lowered case-rate in inoculated and uninoculated. Adding all the figures given, Table I, there are 29 cases of cerebrospinal meningitis in 90,037 inoculated and 211 cases in controls, of which only 70,474 are reported. (2) Termination of epidemic. This depends on the percentage of population inoculated. Where it is only 6% as in Riding and Corkill's figures, the results are poor, but where it is from 50–100% as in Zrūnek and Feierabend, Russell, Sorel, Le Bourdelles and Sedallian, the epidemic is reported to have disappeared.

The dosage of vaccine varied from 1,000 millions to 10,000 millions (in 3 doses). The best results were always obtained with the largest doses.

TABLE I.—HISTORY OF PREVIOUS PROPHYLACTIC INOCULATION IN CEREBROSPINAL MENINGITIS

Reference	Country	No. inoculated	Dosage	Failures	Controls not inoculated	Cases	Year	Remarks
Greenwood	Gt. Britain	4,000	+++	0	..	..	1916	No control group
Gates	U.S.A.	3,702	+++	3	..	..	1918	No control group
Bruynogheand Walwarrens	Belgian Congo	3,000	+++	0	8,000	21	1926	
Bruynogheand Walwarrens	Belgian Congo	14,086	+++	3	3,724	97	1926	100 % inoculation of one group, epidemic disappeared
Le Bourdelles and Sedallian	Belgian Congo	3,004	+++	0	7,867	21	1930	Epidemic disappeared
Zrūnck and Feierabend	Czecko-slovakia	22,180	+++	5	19,684	6	1931	Epidemic much reduced in inoculated garrisons
Riding and Corkill	Sudan	[10,198]	+	[9]	[10,133]	[13]	1932	[Results as published.]
Riding and Corkill	Sudan	10,198	+	9	18,187	34	1932	Amended to include all controls
Yacob	India	3,577	+++	2	3,577	6	1935	Epidemic much reduced
Russell	India	1,768	+++	0	1,768	6	1936	Epidemic much reduced
Saleun and Ceccaldi	French Africa	12,666	+	0	0	0	1936	Epidemic ceased two days after 100% inoculation of population
Sorel	French Africa	5,000	+	0	1,768	15	1937	Epidemic ceased
Maclean and Bevan	Cyprus	6,856	++	7	5,899	5	1938	Epidemic reduced to one-third
	Totals	90,037		29	70,474	211		

LOCAL CONDITIONS

Cyprus is a British Crown Colony situated in the eastern Mediterranean about 40 miles from Asia Minor and 60 from Syria. It has a greatest length from east to west of about 140 miles, a greatest breadth of about 40, and an area of 3,572 square miles. The island consists of a flat, almost treeless alluvial plain, bounded on the north by a narrow range of limestone mountains reaching an altitude of over 3,000 feet and extending eastwards to form the Karpas Peninsula, while a mountain system occupies most of the south and west. These latter mountains, which are of volcanic origin, reach a maximum height of 6,000 feet and in them important deposits of copper, chromium and asbestos occur.

The climate naturally varies considerably in different parts of the island but seasons follow the same cycle as in England. In the plain there is a short mild winter, during which most of the annual rainfall of about 20 in. occurs and the occasional frosts are experienced; the summer is long, dry and intensely hot, but on the sea coast, although the temperatures are lower, the humidity is considerably higher.

The official records for Nicosia, the capital, situated in the central plain, show that the maximum recorded shade temperature during the last fifteen years was 111° F., and the minimum was 26° F. On the southern mountain range snow often lies until May, and even at the height of summer the weather is never uncomfortably hot. The prevailing wind is north-westerly, but during the winter there is often a bitter north-east wind from the highlands of Asia Minor.

The estimated population of the island at the end of 1937 was 372,810, about one-sixth of whom were Turkish-speaking Moslems and the majority of the remainder Greek-speaking members of the Orthodox Church of Cyprus. A number of other religions and languages are represented, including Maronites, Armenians, and Jews. As a rule the population can be easily split up into natural groups according to either religion or language, but as Buxton (1920) has shown, this classification should not be applied strictly to race, for, as judged by anthropomorphic characteristics, the Cypriots, whether Moslem or Christian, are a complex racial mixture.

Although a few small industries are developing in the larger towns, and mining in recent years has begun to be developed on an economic scale, the island is essentially rural, and the great majority of the inhabitants are employed in agriculture, living in small villages and often owning their own houses and land. The main towns are connected by a network of tarred roads, but most of the remaining roads have only a clay surface and are often impassable for motor traffic during the winter. However, there are very few villages that are not served by a road of some sort. Village lorries run regularly to and from many of the villages to the nearest towns, and donkeys and mules are still largely used by the villagers. Itinerant tradesmen, such as butchers, tailors and merchants, travel round from village to village. Some of them were proved to be carriers of meningococci and so they were often an im portant means of spreading infection. The standard of living in Cyprus villages, compared with that in England, is still very low. The style of house varies slightly in different parts of the island, but a typical peasant house is a long, narrow, structure, having a central double door with a shuttered, unglazed window on each side ; the total length might be as much as 40 ft., while the width, which is limited by the length of the available timber, is about 12 ft. In the better class houses a central gothic arch or a number of wooden roof-props form a central supporting ridge for the timbers, so that the area of the house can be considerably increased. The floor is composed of dried mud or slabs of local marble, and the roof, which is almost flat, is made relatively waterproof by a covering of clay. A rough fireplace is usually to be seen in houses in the hill villages. Although the more prosperous villager may have a house containing a number of rooms, the average peasant family lives, eats and sleeps in the one room, which also provides shelter for the animals during the night. This latter custom has the advantage of saving the expense of stables and of providing warmth in winter ; moreover it facilitates the feeding of oxen which is customary during the night. It is usual for two or three members of the family to share the same bed, and at night all doors and windows are closely shut. Although this traditional house results in gross overcrowding inside the family circle, the buildings are cool in summer and relatively warm in winter. There does not appear to be much close contact between villagers outside the immediate family circle, except in the village coffee-shop where most adult males gather for the purposes of gambling, talking, and imbibing Turkish coffee and Cyprus brandy.

There is often considerable overcrowding in these village coffee-shops. Sanitation in villages is practically non-existent. Flies are found everywhere. Water is often scarce in summer and is usually obtained from surface wells, although small local piped supplies are gradually being introduced.

The peasant's diet is largely a vegetarian one, local wholemeal bread and olives being the mainstay, while various types of beans, cucumbers and citrus fruits are eaten as well as rice, potatoes, raisins and almonds. Sheep's and goat's milks are

consumed, chiefly in the form of cheese, but cow's milk is rarely used in the villages ; meat is regarded as rather a luxury and in the average household is eaten about once a fortnight. The diet, although bulky, appears adequate, for deficiency diseases are rarely encountered. There may possibly be some shortage of animal protein, but it can be safely said that nutrition is not a problem of great importance in Cyprus.

As the villagers entirely depend on their various seasonal crops for their existence, borrowing of capital is common, and the difficulties arising as a result of rural debts form one of the much discussed problems of Cyprus.

Malaria is highly endemic in many of the villages because innumerable small pools are left in the dried-up streams which form ideal breeding places for *Anopheles superpictus*. Many villages have an infected spleen-rate of 100%.

In the towns, conditions, though still often primitive, approximate to those found in Eastern Europe. The chief change in recent years is to be seen in the mining towns, the most important being the copper pyrites mines in the locality of Lefka, where the Cyprus Mines Corporation employ about 5,000 people and, so, including the dependants of these, the company is responsible for some 15,000 persons. As a result of considerable expansion of this industry during the last few years, villagers from all parts of the island have been attracted by the chance of relatively high wages, and an abnormal concentration of the population has been the result. Building has not kept pace with this expansion, so that houses are expensive and often difficult to obtain. Consequently, a great many people still live out of doors during the summer, but at the onset of winter they crowd together into the available houses. This was the situation at the end of 1936 when the epidemic of cerebrospinal meningitis started, though, as a result of a recent extensive building programme, conditions have improved considerably. Apart from the people actually living in the immediate vicinity of the mines, a great number live in villages within about 10 miles of these mines and come daily to their work. As most Cypriots are essentially agriculturists, they are usually content to work in the mines for a few months only and then return to their crops, perhaps to seek re-employment in the mines when they have sold their produce and spent the proceeds. This continual change of occupation is an important factor as a result of which the mining company may engage in one month twice as many labourers as are on their average pay roll. The conditions existing in the mining area have increased the spread of infection in the recent epidemic of cerebrospinal meningitis ; for not only has it formed a central nidus of overcrowding during the winter months, but it has enabled persons to introduce the infection into the more distant villages.

For purposes of administration, the island is divided into six districts, each of which has a central town which forms the district headquarters. The Government provides a State Medical Service which is run by a few British and a number of Cypriot doctors, with a Director of Medical Services in administrative control. In each of the six district towns there is a general hospital, and the island also has a leper farm and hospital, a mental hospital, a sanatorium and pathological and analytical laboratory. Malaria, typhoid, bacillary dysentery and trachoma are prevalent, and occur more frequently in rural areas than in the towns. Otherwise, disease incidence is roughly similar to that in Great Britain. Surveillance and medical inspection are carried out at the ports and smallpox, plague, typhus, and cholera, though endemic in the Near East, have not been reported from Cyprus for a number of years. A system of compulsory notification of infectious diseases has been in force since 1931.

The Inoculation Experiment

Cyprus is not an ideal country in which to undertake a careful inoculation experiment. Although the epidemic which occurred in 1936–37 gave rise to widespread consternation, it was difficult to predict how the offer of a prophylactic vaccine by

the Medical Department would be received by the villagers. The Government's plan was to inoculate those villages which had shown a heavy incidence during the previous season, and to leave others uninoculated. We soon found it impossible to adhere to our original plans, because the Government found it necessary to make a small charge for each inoculation. The response in some of the selected villages was very poor, and conversely it was difficult to refuse inoculation to the inhabitants of other villages who were not only willing to pay for the vaccine, but clamoured to be included in the prophylactic experiment. Under the circumstances the best available control was the uninoculated member of the family living in the same house as the inoculated.

Both Corkill (1936) and Manoussakis (1930) claimed to have controlled epidemics by reducing the carrier rate—the former by the administration of vitamin A, and the latter by prophylactic inoculation. It seemed advisable to confirm their work and observe the effect on the epidemic by varying the percentage of the population inoculated.

A census was therefore made of all villages inoculated, and a record kept of the number of individuals inoculated in each village. The inoculation and record keeping were carried out by a team which toured the villages under one of us (C.E.B.), then a District Medical Officer. The team consisted of an English District Medical Officer and nursing sister, and a Cypriot staff of two medical officers, a nurse, an accountant, five clerks and three policemen who maintained order. The team travelled by lorry, and visited the villages in Nicosia, Limassol and Paphos Districts, which appeared to have been serious foci of infection during the preceding winter. Although villagers were informed beforehand of the date of the arrival of the team in their village it was usually necessary to spend considerable time and energy on propaganda to ensure a good attendance. The inoculation was carried out in local schoolrooms or coffee shops. Every individual who applied for inoculation had his particulars written down by one of the clerks on a special serially numbered card. A record of the name, age and sex not only of each inoculated individual but also of the other persons living in the same house was made. This was done on the card of only one person out of every household represented. Between the first injection and the second one ten days later, an alphabetical list was made of all inoculated persons in each village visited. By a system of cross reference it was then a simple matter to find out for any inoculated individual how many persons lived in the same house and how many of these had not been inoculated. The latter formed the control group. The Government team worked from October 4 to November 18, 1937, by which time it had inoculated 6,856 people.

While the team was touring the villages Dr. P. Smitten, Medical Officer of the Cyprus Mines Corporation, had already started to inoculate the employees at the mines and as many as possible of their wives and families. This continued for the greater part of the epidemic season, as the company was continually taking on new labour. These two campaigns were run quite independently but we are indebted to Dr. Smitten for the details of all those inoculated by him. At his suggestion all individuals who were inoculated received a minute intradermal injection of 25% solution of Indian ink into the scapular region for each dose of vaccine administered. This produced a permanent tattoo mark ; and, except for two cases injected on the first day of the campaign in which slight skin necrosis occurred, no complications were observed.

The inoculation campaign of the Cyprus Mines Corporation started at the end of September 1937, and the greater part of the work was completed during October and November, although a certain number of inoculations were still being done throughout the whole season. Over 6,000 persons connected with the mines were inoculated by the end of 1937.

For local administrative reasons a great number of people were inoculated who

were outside the sphere of the experiment as originally planned. The rough figures are given here, but the results of these other inoculations are not discussed further owing to the impossibility of making reliable analysis. Thus, over 5,000 people were inoculated in the six district towns and nearly 8,000 school children scattered throughout Limassol and Paphos Districts. Including the above and eight villages that were inoculated during December 1937 and January 1938, together with a number of secondary schools, prisons, and two other mining concerns, over 30,000 persons received the inoculation course of two injections. This amounts to about 8% of the estimated population of the island in 1937. Over 12% of the inhabitants of the Districts of Nicosia, Limassol and Paphos, which contained the bulk of the cases during the first wave, were inoculated. The position of the various inoculated centres are shown in Map 4, with the exception of the school children in Limassol and Paphos Districts.

During the 12-month period starting from October 1, 1936, there were 836 cases and 284 deaths reported in the whole island, while in the next twelve months starting from October 1, 1937 (i.e. including and following the inoculation campaign), 298 cases and 81 deaths occurred. That is to say that the incidence of the disease during the second wave was reduced to 36% of that of the first wave, and the number of deaths to 29%.

During the third wave up to the end of May 1939 there were 123 cases reported and the deaths were 51. An occasional case may occur during the rest of the third period which finishes at the end of September 1939, but judging from past experience the final figures for the third period will not alter much from those quoted above. It will be noticed that there is only a slight fall in the death-rate in the second period and this in spite of the fact that during the second wave of the epidemic there was the additional help of sulphanilamide in the treatment of the disease. It must therefore be recognized that although the number of cases was greatly reduced, those cases which did occur were more severe clinically than those of the first wave. We think that this increase in the severity of the disease fits in quite well with the suggestion made later in the paper that in the presence of prophylactic inoculation only strains of increased virulence are capable of causing cerebrospinal meningitis.

When we try to account for the marked fall in the total number of cases during the second period we find that conditions were equally favourable during both years for the continuance of the epidemic. As shown in Graph I meteorological conditions appear to be little altered in the two periods. There had been some improvement in the housing conditions in the actual mining towns, but this did not affect the great bulk of the mining population who lived in neighbouring overcrowded villages. The great reduction in the number of cases between the two waves was just as marked in these villages as in the improved housing area of the towns. We were led to expect from the 1908–1910 epidemic in Cyprus and also from the history of recent epidemics of this disease in contiguous countries such as Egypt and Asia Minor that the case incidence would be just as great in the second year as in the first. We think it unlikely that we were fortunate enough to start our inoculation campaign when the epidemic was subsiding and so be led to a false conclusion. With the exception of the three district towns and one mining centre, no inoculations were performed in the Famagusta, Larnaca and Kyrenia Districts: the population of which amounts to over one-third of that of the whole island. These three districts had 48 cases during the first wave, and 78 during the second. Therefore, although the epidemic as a whole has been considerably reduced, this reduction has been limited to the inoculated area, while in the non-inoculated area, the incidence, though small, has actually increased.

The results of the original experiment are set out in Table II which gives the cases and deaths occurring in the twelve months following October 1, 1937. Care has been taken to exclude from the control group all persons who, subsequent to the visit of the Government team to their villages, were later inoculated by the Cyprus Mines

TABLE II.—INCIDENCE OF CEREBROSPINAL MENINGITIS, 1937–38, IN INOCULATED AND CONTROL GROUPS.

	Population at risk	Cases	Cases per 1,000	Deaths
Inoculated ..	6,856	7	1·0	1
Controls ..	5,899	5	0·9	0

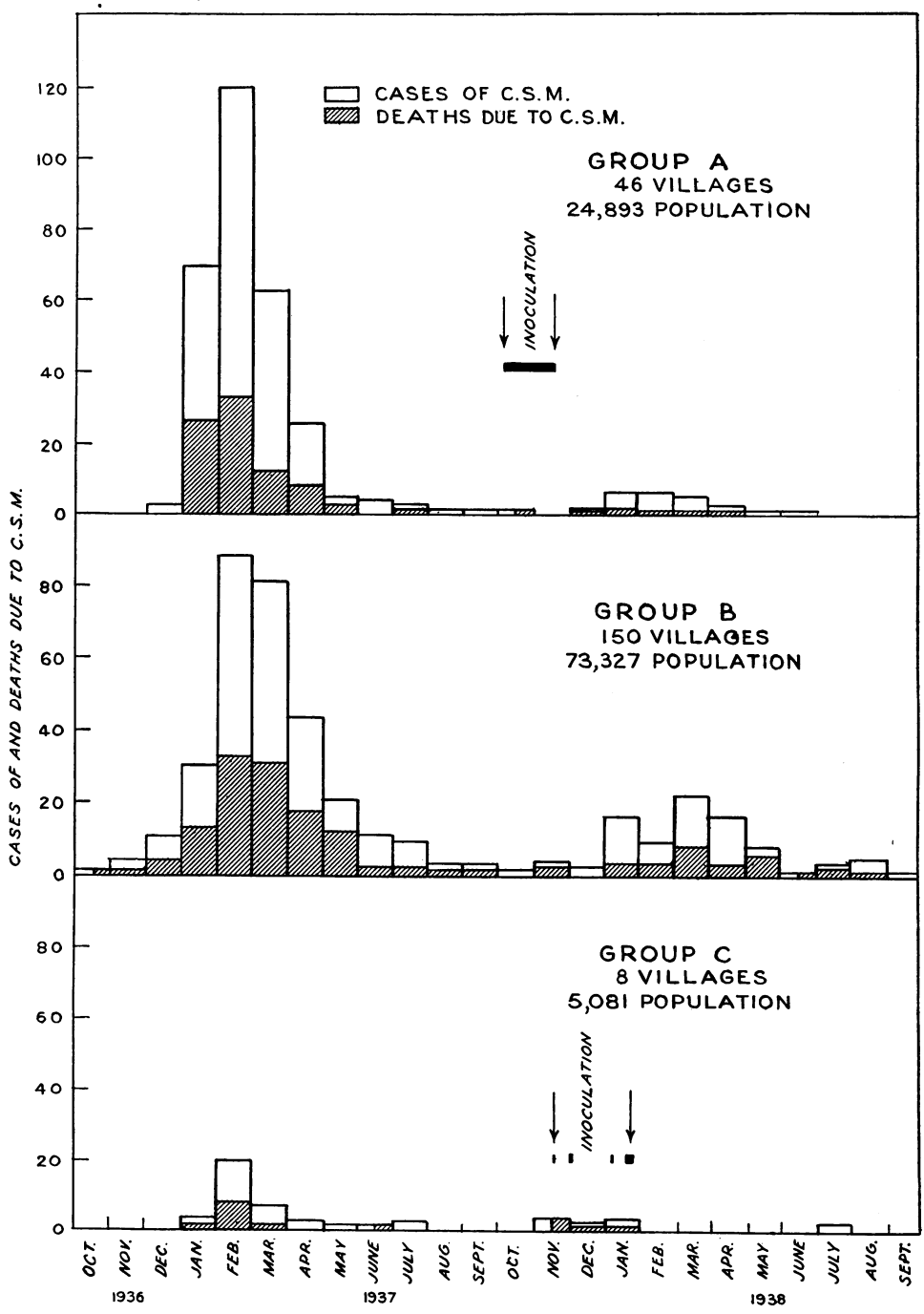
Corporation. Only those individuals who received two injections are considered. It shows that the case incidence in both groups is very small, there being no significant difference between the two groups. Reference to Graph I shows that the incidence of the disease had dropped very considerably although the reduction was much more marked in the three districts under consideration. The distribution of the cases is shown on Maps 1, 2, and 3.

The reduction in the inoculated area seemed to be so marked that a closer analysis has been made. As already mentioned, a census was made of the villages inoculated by the team, but unfortunately it has not been possible to get this done for all the villages where cases had occurred during the first wave. The population of these other villages was therefore obtained by calculating the annual increase from populations given in the 1921 and 1931 Census Reports. The actual mining towns are excluded from this analysis, owing to the improvement in housing that had been made after the first wave and the very considerable movements of the population that were continually taking place. By combining the figures of the Government team and the details obtained from the Cyprus Mines Corporation it was possible to determine the total number of persons inoculated in every village and so the percentage inoculation of each village. The results for Nicosia, Limassol and Paphos Districts are set out in Table III and Graph II. The first wave includes cases notified in the twelve months from October 1, 1936, and the second wave cases from October 1, 1937. The data are taken from the official notification cards which are dated, on the average, about one week after the date of onset of disease. Group A villages have 10% or more of the inhabitants inoculated, the maximum figure for any village being 72%. The figures are derived from 5,824 persons inoculated by the team and 1,373 by the mines. The majority of Group B villages were not inoculated, although one village had 7% of its inhabitants inoculated, and the next highest village had 4%. A number of them probably had one or two persons inoculated who had returned from the mines ; the group as a whole, however, can be regarded as non-inoculated. There were eight villages which according to the original plan would not have been inoculated, but for reasons explained earlier it was often impossible to adhere strictly to this programme. These eight villages—Group C—were inoculated as follows, one in November, three in December 1937, and four in January 1938, immediately following the notification of the only cases that occurred in these villages. Table III and Graph II, therefore, contain every village which had a case of cerebrospinal meningitis during the first wave ; the only cases that are excluded are those occurring in the three district towns and in the actual mining centres.

TABLE III.—INCIDENCE OF CEREBROSPINAL MENINGITIS IN INOCULATED (GROUP A), NON-INOCULATED (GROUP B) AND LATE INOCULATED (GROUP C)* VILLAGES.

Group	Number of villages	Population	Cases		Cases	Cases per 1,000	
			1st wave	← Prophylactic Inoculation	2nd wave	1st wave	2nd wave
A	46	24,893	296		27	11·9	1·08
B	150	73,327	308		83	4·2	1·13
C	8	5,081	36		9	7·1	1·77

* These villages were inoculated during the epidemic period.



GRAPH II.—Inoculation experiment. Groups as in Table III.

The figures show a considerable reduction in the number of cases in both groups in the second wave as compared with the first. This reduction is to one-eleventh in the cases of Group A, and to less than a quarter in Group B. In Group C during the first wave there was a typical curve with the maximum number of cases in February, but during the second wave the epidemic stopped quite suddenly in January, following inoculation. In considering the comparatively high incidence during the second wave in this group it must be remembered that most of the cases occurred before inoculation.

The results show that there has a been a general reduction in the number of cases in all the areas. As the greater reduction in Group A villages may have been due to the acquired immunity of the susceptible individuals as a result of the high incidence during the first wave, it is not claimed that inoculation was the sole cause in this reduction. As against this the course of the epidemic in the mining town is interesting. Inoculation was carried out in this area until the expected peak of the epidemic in February and March 1938. After a big campaign in October and November 1937, the inoculation was largely confined to fresh recruits who during the second period there have provided a continual influx of new and presumably susceptible people to the mining area. Most of these were inoculated on arrival. In spite of the influx there was a reduction from 75 to nine cases. Since it has been impossible to obtain an accurate census of these towns, because of the recent expansion, calculations from the census are misleading. A rough estimate of the population, however, would be about 10,000 which would give 7·5 and 0·9 cases per 1,000 during the first and second waves respectively. This reduction is much greater than in the Group B (non-inoculated villages), shown in Table III.

In order to attempt to separate these various factors the villages shown in Table III have been further subdivided. In Table IV all villages with over 20 cases per 1,000

TABLE IV.—INCIDENCE OF CEREBROSPINAL MENINGITIS IN "INOCULATED" (A1 AND A2) AND "NON-INOCULATED" (B) VILLAGES ARRANGED ACCORDING TO INCIDENCE AND AMOUNT OF INOCULATION.

Group	No. of villages	Population	Cases		Cases per 1,000	
			1st wave	2nd wave	1st wave	2nd wave
(0–) A1 (heavy)	3	1,875	6	0	3·2	0·0
A2 (light)	6	3,712	13	2	3·5	0·54
B	84	56,494	137	54	2·4	0·96
(5–) A1 (heavy)	6	3,559	23	3	6·4	0·83
A2 (light)	6	4,782	30	7	6·3	1·46
B	36	11,629	76	16	6·6	1·37
(10–20) A1 (heavy)	6	4,000	57	5	14·3	1·25
A2 (light)	8	3,192	48	9	15·0	2·82
B	25	5,484	73	14	13·3	2·55

A1 = villages with over 30% of the population inoculated.
A2– = villages with under 30% of the population inoculated.
0– = villages where there were less than 5 cases per 1,000 during the first wave.
5– = villages where there were more than 5 but less than 10 cases per 1,000 during the first wave.
10–20 = villages where there were 10–20 cases per 1,000 during the first wave.

during the first wave have been excluded in order to eliminate the effect of any possible rise in resistance of the population. The remaining villages have been divided according to the incidence during the first wave into groups with 0–, 5- and 10–20 cases per 1,000 of the population living during the first wave. The villages in Group A of Table III have been further divided into: Group A1, heavily inoculated villages (30–72%); and Group A2, lightly inoculated villages (under 30%). It can be seen that in all groups there is a very considerable reduction in incidence in the second wave compared with the first. When rates of 20 per 1,000 and under are considered,

villages with a high incidence in the first wave tend to have a comparatively high incidence in the second wave. All the groups in Table IV have comparable figures in both waves except Group A1 in the second wave where the reduction is much better than in either of the other two groups. This reduction in the heavily inoculated Group A1 is always 100% better at least than in either of the other uninoculated or inoculated groups. This suggests that prophylactic inoculation has some effect in reducing the incidence of the disease. However, we are aware that our inoculation experiment was not perfect and open to criticism, and we therefore cannot claim that prophylactic inoculation was the sole cause of the better results obtained in the second wave. The various groups were not equal in number nor were they pre-selected. Also, owing to the limitations of our experiment the inevitable patchy distribution of inoculated persons, even in highly inoculated villages, would enable cases of the disease to occur as a result of contact with many non-vaccinated individuals. In view of these fallacies it does not seem advisable to apply tests of significance to any of our figures, and no final conclusions can be drawn. We do, however, consider that our results are compatible with a prophylactic vaccine being effective in controlling an epidemic of cerebrospinal meningitis, although we wish to state that statistically we have been unable to prove our point.

The Preparation of the Vaccine

It was impossible to examine serologically many of the strains which occurred during the epidemic. Twenty strains were tested with the Oxford Standard Group I and II sera, and twelve of these gave good agglutination to a titre of at least 1 : 100 with Group II and none to 1 : 50 with Group I. Eight strains were labelled inagglutinable as no agglutination occurred with these strains at a titre of 1 : 10. Unfortunately, a large number of strains brought home to England did not survive the journey and the opportunity for further serological work was lost.

The vaccine used in Cyprus was supplied by Messrs. Parke, Davis & Co., London. It contained 14 strains of meningococci belonging to Gordon's Types I, II and III. No Type IV was available in England at that time nor were any of the local strains from Cyprus. All the strains were supplied by Dr. Scott of the Ministry of Health Laboratories, London. The vaccine was grown for twenty-four hours on boiled blood-serum agar and killed by heat for one hour at 60° C. and sent out at 1,000 million organisms per cubic centimetre. The dosage was $\frac{1}{2}$ c.c. and 1 c.c. at ten days' interval. Any reactions which occurred were slight and no serious accidents of vaccination were reported by the team.

In view of our few inoculated failures we recommend a larger dosage for use in future—2,000, 4,000, 4,000 millions at weekly intervals. The vaccine should be made from recently isolated strains and kept in cold storage until just before use, so as to prevent autolysis.

The Occurrence of Cerebrospinal Meningitis in Inoculated People

There were 14 cases of meningitis reported in inoculated people up to the end of April 1938, i.e. during the time of the survey. Two of these cases died : one in twelve hours, before any bacteriological examinations could take place. The other died in six days, and her illness was complicated by lobar pneumonia : pneumococci and meningococci being found in her cerebrospinal fluid.

Of the other 12, two were definitely diagnosed as pneumococcal ; one had pneumococci and meningococci in the cerebrospinal fluid, and in five more cases which occurred in the outlying districts no material was sent to the laboratory for diagnosis. Accordingly only seven out of 14 were diagnosed definitely as being

meningococcal. Of these three were complicated by the presence of pneumococci. The impression left was that cases of cerebrospinal meningitis occurring in inoculated people were more severe than in the non-inoculated. The vaccine did not prevent the occurrence of complications, as two of the cases had meningococcal arthritis, and one of these also had an orchitis.

Epidemiology of Cerebrospinal Meningitis as Found in Cyprus

Epidemic cerebrospinal meningitis occurs especially during the late winter and spring ; that is, in the season of nasopharyngeal catarrhs, pneumonia, and influenza. The weather at the time of the epidemic is usually colder and wetter than normal for the locality. Many people have shown that during an epidemic of catarrhs the carrier rate for meningococci rises quickly and in spurts. In a susceptible community this sudden increase in the carrier rate is often accompanied by cerebrospinal meningitis, but, as stated by Dudley and Brennan (1934), this is not necessarily so. They swabbed the inhabitants of two naval garrisons at fortnightly intervals for a period of fourteen months. Chatham had a carrier rate of 50% with no cases of meningitis ; Portsmouth had a carrier rate of 5% with six cases of meningitis. They explain this by surmising that at Chatham there was a strain of great infectivity but of low invasiveness, while at Portsmouth the strain was of high invasiveness but low infectivity.

While the carrier rate is high we presume that the meningococci are being rapidly passaged from man to man. We know from experiments that if the meningococcus is rapidly passaged through animals in the presence of mucin it quickly gains in virulence. Thompson (1920) also claimed to have observed this increase in virulence during the sudden increase in the carrier rate in human beings. Laybourn (1936) found that it was possible during catarrhal periods for the meningococcus to make a daily change of host ; if at each change it gains only a little in virulence it will eventually reach a susceptible person with sufficient virulence to cause him to contract cerebrospinal meningitis.

In discussing the passage of the meningococcus the Ministry of Health Report on Cerebrospinal Meningitis, No. 65, says :

> "While the transmission of the meningococcus from person to person is common, it is unusual for a patient to have been infected by another patient suffering from cerebrospinal fever. For every case of meningococcus infection which results in cerebrospinal fever, there are many more which do not. Neither the one class nor the other may ever have been in known contact with a cerebrospinal fever patient ; they have derived their infection from persons who, if they have been ill at all, have shown no certain signs of infection of the cerebrospinal system. In other words, the great majority of infections are derived from persons who, for the time being, are unrecognized carriers of the meningococcus."

Arkwright (1915) concluded that :

> "Meningococcal infection is not so much an epidemic of cerebrospinal meningitis as an epidemic of saprophytic meningococci in the nasopharynx—cerebrospinal meningitis is an epiphenomenon associated with increased virulence."

Neither of these last two authorities explains why the "epiphenomenon" of cerebrospinal meningitis suddenly occurs but we suggest that it is possibly due to the increased virulence of the meningococcus which it acquires during its rapid passage from man to man. In Cyprus, we recorded many instances of the rapid transference of catarrh inside the family circle, and it was noticeable that it was only the last victims of the common infection who developed meningitis. Unfortunately, as these histories could only be obtained after the cases had occurred we have no

bacteriological confirmation that the meningococcus was being passaged with the other catarrhal organisms. Luckily, while carrying out routine swabbing in an epidemic area we were able in a case of cerebrospinal meningitis to demonstrate the rapid passage of the meningococcus in association with catarrh (Table V). The village had suffered from an epidemic of catarrh for three weeks during which cases of cerebrospinal meningitis had occurred. Bi-weekly swabbings were being done of all contacts and in the families of last year's cases.

TABLE V.—A CASE OF CEREBROSPINAL MENINGITIS FOLLOWING RAPID PASSAGE OF MENINGOCOCCI.

Subject	Age	Previous history	Swabs for meningococci 1938		
			Feb. 2	Feb. 5	Feb. 9
Boy	5	Case cerebrospinal meningitis, 1937	+	+	+
Girl	9	Carrier, 1937	+	—	—
Baby	5/12	..	—	+	+
Mother	29	..	—	—	+
Father	30	Nursed son during 1937	Away from home	Away from home	+ Developed cerebrospinal meningitis Feb. 11

The father was away from home attending his sheep for ten days. He returned home after the meningococcus had reached the fourth member of the family. He did not associate with anyone else in the village and contracted cerebrospinal meningitis three days after returning home. Two people who associated with him after he was attacked developed cerebrospinal meningitis within a few days.

We know that there is great variation in the susceptibility of different people to cerebrospinal meningitis. This difference in immunity may be artificial ; for example, by reason of fatigue, excessive use of alcohol, dust, concurrent disease ; or it may be actual, for example in the youngest members of the family, new recruits, shepherds, &c. If we concede that immunity can be artificially raised by vaccines—Sophian and Black (1912), Kolmer and Rule (1938), it is reasonable to suppose that prophylactic inoculation will reduce the number of susceptibles in a given population.

In the review of prophylactic inoculation against cerebrospinal meningitis quoted above, we see that there have been three cases per 1,000 inoculated, which compares favourably with the failure rate in antityphoid inoculation of 5·6 per 1,000 (Antityphoid Committee, 1913). If our contention that *rapid passage* increases the virulence of a meningococcus is valid, then there must come a stage when even a well-immunized man will meet a strain of meningococcus whose invasiveness is so increased that he will succumb to cerebrospinal meningitis.

In England, where the carrier rate is high in winter, there must be a fair degree of immunization taking place ; in Cyprus and in the tropics, where the carrier rate is low (1% to 2%, with an increase to only 5% to 10% in epidemic periods), there is less chance of acquiring immunity. In support of this, we note that England has only a few sporadic cases, as compared with the much higher morbidity in Cyprus and the Tropics. Where the carrier rate returns to a low level for most of the year the disease occurs in epidemic proportions. We suggest that the greater the proportion of the population that are inoculated the better are the chances of preventing the epidemic. We would go so far as to propose that the surest way of preventing the *rapid passage* of the meningococcus in a community is to inoculate the whole population.

In view of the accepted association between epidemics of cerebrospinal meningitis and epidemics of influenza and catarrhal infections, we must consider whether it

would be advisable to employ specific measures to prevent epidemic catarrhs occurring in the presence of chronic meningococcal carriers. It would be interesting to see whether a vaccine, consisting not only of meningococci but also of all the usual catarrhal organisms, would be more effective than a plain meningococcal vaccine in controlling both the carrier rate and the incidence of meningitis. We know that vaccination will not sterilize a chronic carrier, but it is conceivable that large scale prophylactic vaccination among his contacts would limit his potential infecting power. It may require many passages from the carrier before his avirulent strain acquires sufficient virulence to cause meningitis.

Conclusion

In view of the evidence that is put forward that this disease may be spread by *rapid passage*, and the suggestion that wide scale inoculation might limit this phenomenon and so indirectly control an epidemic, we consider that no satisfactory experiment has yet been published. In this criticism we include our own work. We therefore make the following suggestions as to how, in our opinion, an experiment should be conducted in the hope of arriving at more conclusive results:

(1) The carrier rate of a number of "islets" of the population should be determined before starting the inoculation campaign.

(2) The "islets" should then be divided into two known groups, which should be equal in all respects, including the carrier rate at the time and previous experience of the disease. There should be no direct communication between the two groups.

(3) One group should be 100% inoculated and no inoculations should be done in the other group. All inoculations should be free of charge and compulsory.

(4) The vaccine should contain local strains of meningococci and common catarrhal organisms.

(5) The *complete weekly carrier rate* of each group should be determined for the whole season starting from the day of inoculation.

(6) The introduction of carriers and new arrivals from outside the groups should be limited as far as possible.

(7) In every case occurring in the groups the patient's movements during the incubation period should be carefully investigated, and all possible contacts swabbed with the object of determining any sources of infection introduced from outside the group.

(8) A full-time bacteriologist with a laboratory within easy reach of the groups under observation is necessary for reliable results. Experience has shown us that not more than 50 specimens a day can be dealt with satisfactorily.

(9) If the results of such an experiment appeared favourable it might be worth repeating the work with a different percentage of the groups inoculated. In this case the inoculated persons should be distributed evenly throughout the group.

We have to thank the Government of Cyprus for the invitation to take part in this experiment and especially the Director of Medical Services and the Government Pathologist for their very ready collaboration and advice; also the Committee of the Inoculation Department of St. Mary's Hospital who granted the necessary leave and bore the expense of sending one of us to the scene of the epidemic; and lastly Dr. P. Smitten, medical officer of the Cyprus Mines Co., who fitted in so well with our plans and gave us inspiration and support throughout the whole of the period.

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Discussion.—Dr. J. D. ROLLESTON said that he had listened with much interest to the paper as comparatively few publications on the prophylaxis of cerebrospinal fever had appeared. He referred to the paper by Major Greenwood read many years ago before the Section relating that of 4,000 persons inoculated none had developed the disease. Bruynoghe, who carried out vaccination against cerebrospinal fever in the Belgian Congo, reported that the disease was at least ten times less frequent among those given three injections of the vaccine than among the controls. On the other hand active immunization carried out on a large scale by Zrūnek and Feierabend in the Czechoslovak army proved ineffective, as the incidence of the disease was little less among the inoculated than among the controls. Apart from the actual occurrence of epidemics, Terry and Steele had tested 605 children with a meningococcus toxin of whom 66·8% gave a negative reaction after being retested.

Dr. Rolleston said that it was obvious that in addition to active immunization other prophylactic measures were required, especially improvement in hygiene. He asked if the radio and cinema had been used for this purpose or if health visitors were employed in Cyprus.

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Professor ALEXANDER FLEMING congratulated the authors on a fine piece of work and expressed the opinion that in view of the results obtained in Cyprus it was very desirable that other similar observations should be made. It seemed to be brought out that in an investigation of this sort the authorities should not stint facilities and especially laboratory facilities, if the best results are to be obtained. Listening to the paper he had gathered that the authors started with an ambitious laboratory programme but as the epidemic progressed more and more of it had to be dropped and if another such experiment is made there should be a larger pathological staff so that the various problems could be investigated on the spot.

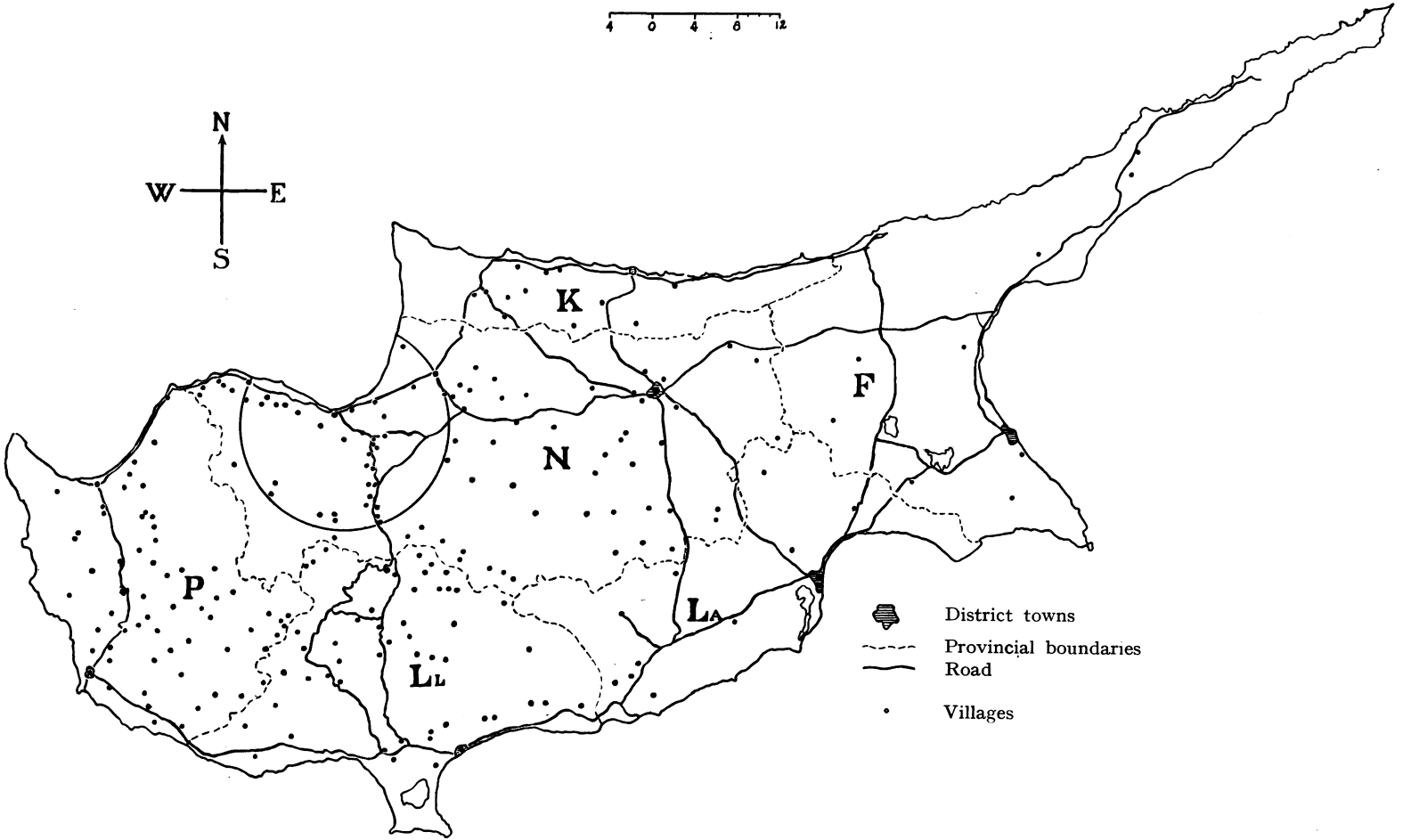
Dr. H. STANLEY BANKS asked whether the type of meningococcus isolated from carriers had been determined. He understood that meningococci of Group II and anomalous types isolated from healthy people were frequently harmless saprophytes. In the cases inoculated during the currency of the epidemic, had any evidence been obtained of the influence of the "negative phase" as a predisposing cause of the disease? He inquired also what opinion was formed of the efficacy of the drug treatment of the disease and what was the dosage employed.

Lieutenant-Colonel J. S. K. BOYD said that it seemed possible that there were circumstances, other than those commonly recognized, which played a part in causing or preventing an outbreak of cerebrospinal meningitis. He recalled an occasion in Simla in 1935, when the stage seemed set for a serious outbreak, yet none occurred. All the conditions postulated by previous speakers were present—overcrowding of the worst kind, a low standard of living, severe physical exertion (for man there is the beast of burden), high humidity, a prevalence of catarrh, and a swollen population consisting partly of immigrant coolies from cities of the United Provinces and Punjab where there was at that time a severe outbreak of cerebrospinal meningitis, and partly of unsalted hillmen from the mountainous hinterlands. The occurrence of two or three cases proved the presence of the infective agent: the absence of any further manifestations suggested that some essential factor necessary for the establishment of widespread infection, additional to those already mentioned, was lacking.

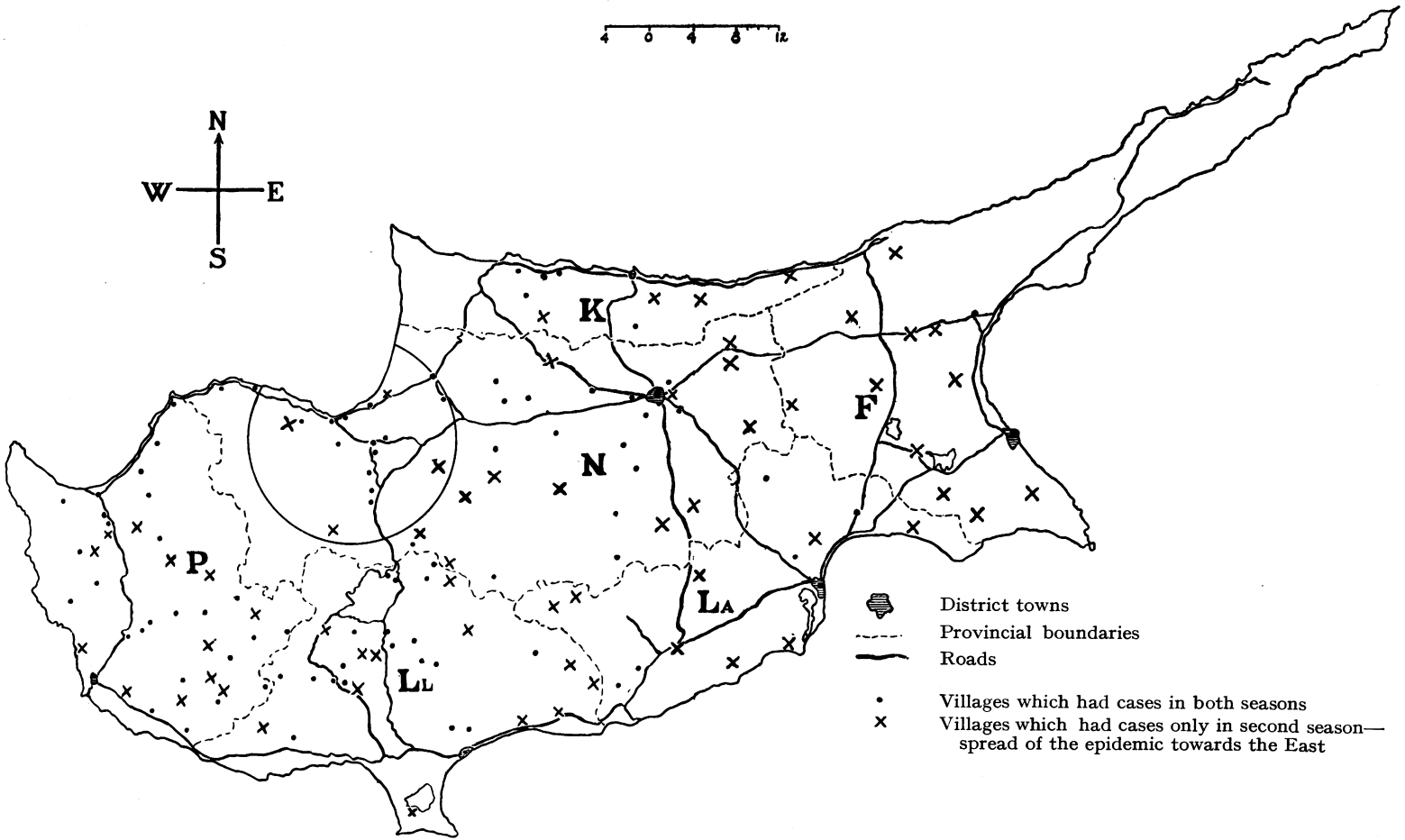
Dr. MACLEAN (in reply) disagreed with Dr. Rolleston that Zrũnek and Feierabend had failed with preventive inoculation. As stated in this paper they had been quite successful where 50% of the population had been inoculated. Their conclusions were too modest and not in agreement with the facts stated in their paper. There is no local radio nor is there a village cinema. The schoolmaster made a very good health propaganda agent.

In reply to Dr. Banks, Dr. MacLean said that some of the strains isolated from carriers were proved to be Group II, but most of them were inagglutinable. There were no means of testing the virulence of individual strains locally. No cases of "negative phase" were noticed after the vaccine, in fact even when the disease was present in the neighbourhood there were no severe reactions. The treatment of cerebrospinal meningitis by the sulphanilamide group of drugs was to be fully reported elsewhere. It is sufficient here to say that it was a great success when given in adequate doses early in the disease. The failures of the drug treatment were in the most virulent forms of the disease where the treatment had to be delayed. The dosage was small when compared with European dosage (1 — 2·5 grm. per day for four to five days) and there was usually a period about the tenth day when the disease tended to relapse and the drug had to be repeated for a few days.

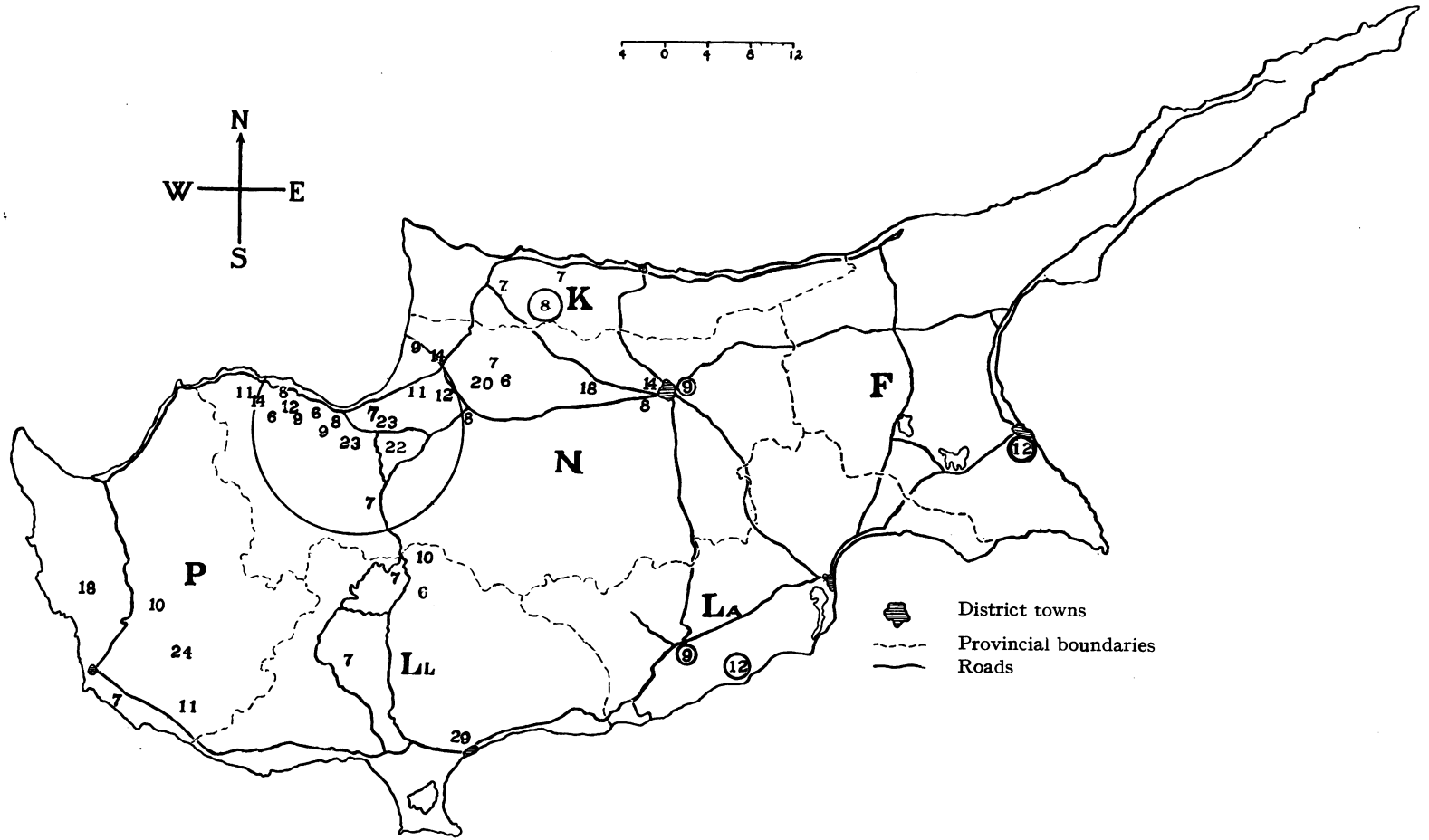
In answer to Lieutenant-Colonel Boyd, he thought that conditions at Simla in 1935 must have been similar to those in Chatham in 1934 as reported by Dudley and Brennan.



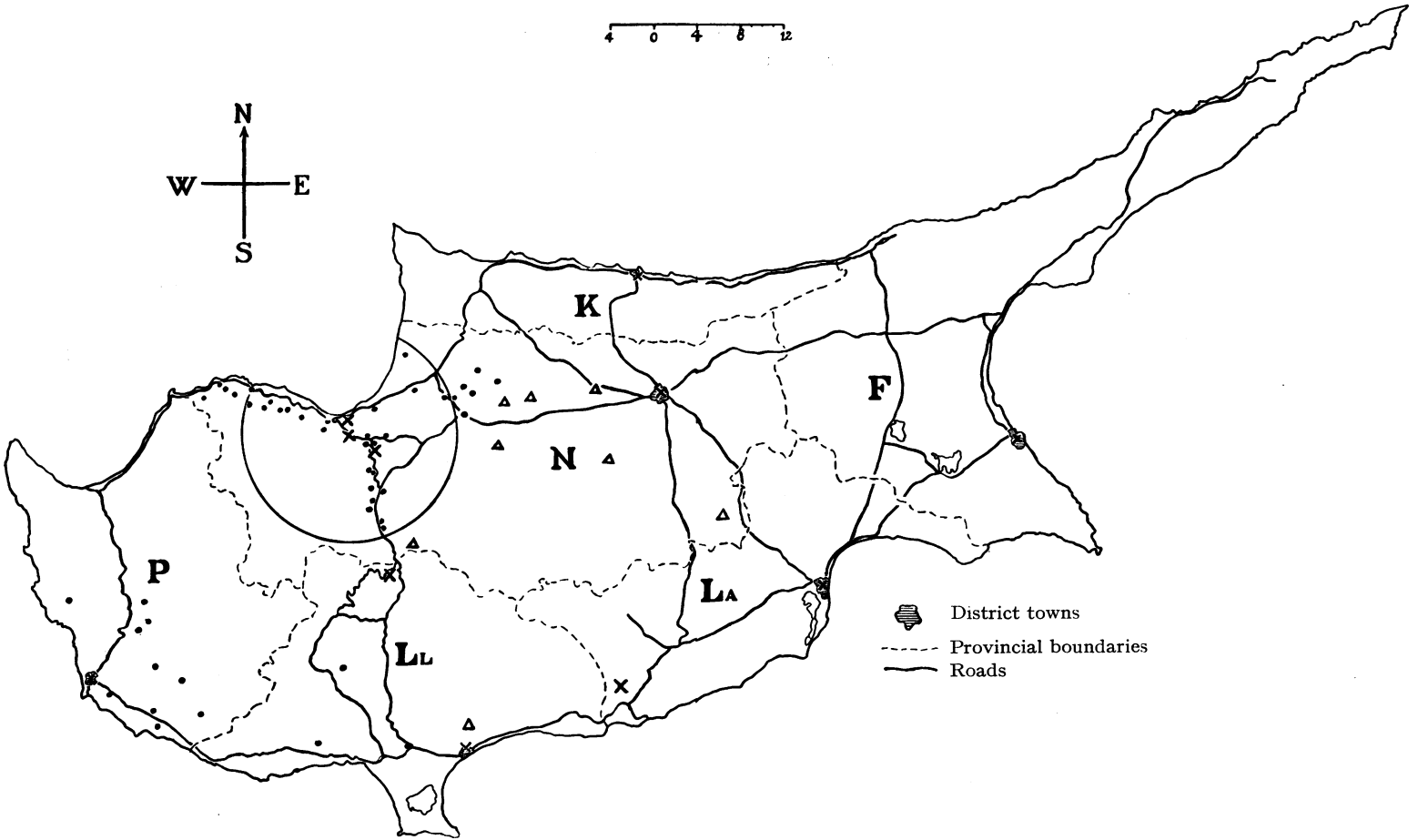
MAP 1.—Cyprus. Distribution of cases of cerebrospinal meningitis during first season (1936-37) by villages. Area inside circle is the mining area which was the principal focus of infection (*see also* Map 3).
K, N, F, La, Ll, and P represent the districts of Kyrenia, Nicosia, Famagusta, Larnaca, Limassol, and Paphos.



MAP 2.—Distribution of cases of cerebrospinal meningitis during second season (1937-38).



MAP 3.—Distribution of cases of cerebrospinal meningitis (1936-38). Only villages with more than five cases are shown.
Figures represent number of cases in village during first season only, e.g. 12.
Figures in circles represent number of cases in village during second season only, e.g. (12).



MAP 4.—Inoculation experiment.

- • Villages chosen by team for inoculation (October 4—November 18, 1937).
- △ Villages inoculated December 1937—February 1938.
- × Other towns and centres inoculated, but outside the experiment.