PROPHYLACTIC VACCINATION IN EPIDEMIC MENINGOCOCCAL MENINGITIS.

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(With a Map and 2 Graphs.)

The dry and dusty period of the year, so conducive to catarrhal conditions of the nasopharynx, is associated in the Northern Sudan with outbreaks of meningococcal meningitis.

The control of these outbreaks presents a formidable problem to the sanitarian, and throws a heavy task upon the physician.

It is in the control of those epidemic diseases of man and animals, in which sanitary science finds itself incapable of attacking effectively the infected sources, or of controlling the spread of the infective agent, that active immunisation has found its principal field of usefulness.

Recent work with regard to the influence of efficient vaccination on herd infection suggests that, where the risk of infection is limited in time, the advantage afforded by vaccination might well make the difference between effective immunity and death.

Prophylactic vaccination in meningococcal meningitis has been tried on only a very limited scale and, as the numbers at risk are great while the morbidity rate of the disease is low, its value has been difficult to assess.

The use of meningococcal vaccines in the production of anti-endotoxin and protective serums in animals is a prolonged and uncertain procedure, but it is reasonable to expect that the injection of meningococcal vaccine into man might at least act as the primary stimulus in the establishment of a basal immunity.

Faced with an epidemic of meningococcal meningitis in Khartoum Province the writers determined to carry out a large scale experiment in prophylactic vaccination.

The field of experiment.

Khartoum Province is a unique field for an epidemiological experiment. It consists of a semi-desert area through which the Nile, with its two tributaries the Blue Nile and White Nile, runs.

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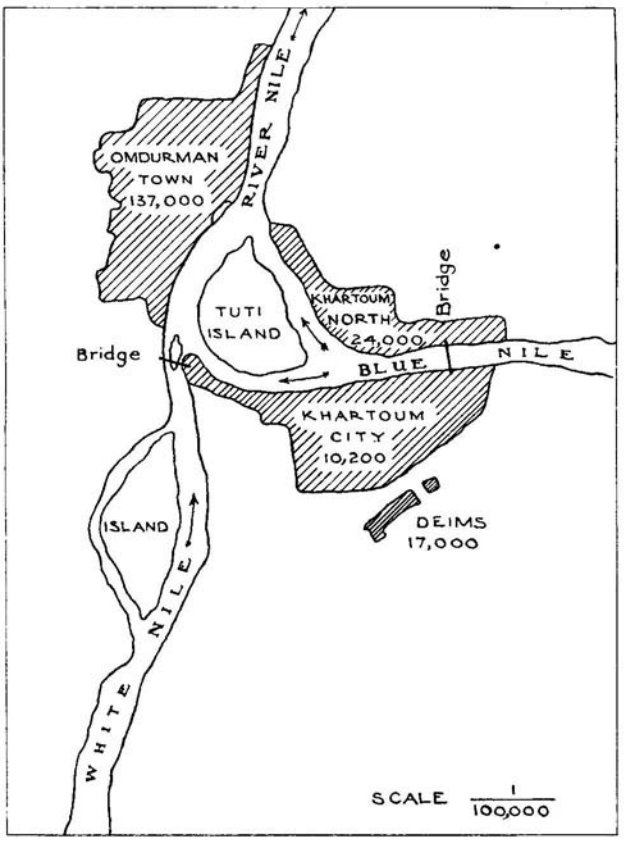
The native population is collected into the city of Khartoum, the townships of Omdurman and Khartoum North, a large village, the Deims, and a number of small scattered village communities.

Overcrowding is the rule in the native houses, which are in the main dark and badly ventilated.

The native population of Khartoum forms practically a closed community, as the rate of immigration is negligible.



Map showing distribution of population in Khartoum City, Omdurman and Khartoum North.

There has been no epidemic of cerebro-spinal meningitis in Khartoum Province in the last 20 years, so it is probable that, as a result of the absence of epidemic experience, the degree of active immunity possessed by the native community, at the commencement of the epidemic to be described, was low.

The accompanying map shows the distribution of the population in the towns.

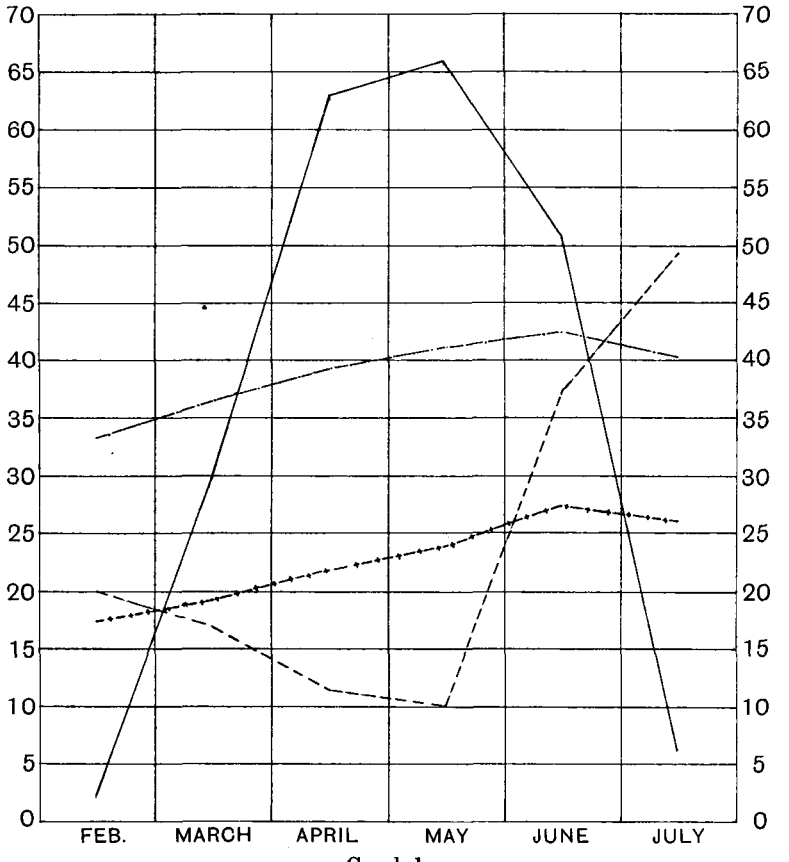
THE EPIDEMIC.

The first cases of meningococcal meningitis occurred on February 28th, 1931, and by March 28th the disease had assumed epidemic proportions.

The epidemic wave passed from the Deims to Khartoum City and Khar-

toum North, and then on to Omdurman and the scattered villages of the Province. It lasted 21 weeks in all, there being 218 cases of the disease notified during this period with 145 deaths.

An estimate of the native population of Khartoum Province is given in Table I, and this indicates that there are more adult females than adult males.



Graph 1.

——————— Cases of Meningococcal Meningitis
– – – – – – – Percentage humidity (average)
–•–•–•–•– Average maximum temperature °C.
–+–+–+–+– Average minimum temperature °C.

The relation of the humidity, and maximum and minimum day temperatures, to the rise and fall of the epidemic is shown in Graph 1.

Table I. *Estimated native population of Khartoum Province.*

Place	Children	Female adults	Male adults	Total
Khartoum City	2,500	4,200	3,500	10,200
Deims	6,000	6,000	5,000	17,000
Khartoum North	8,500	8,300	7,200	24,000
Omdurman	45,000	53,000	39,000	137,000
Various villages	25,000	30,000	23,000	78,000
Totals	87,000	101,500	77,700	266,200

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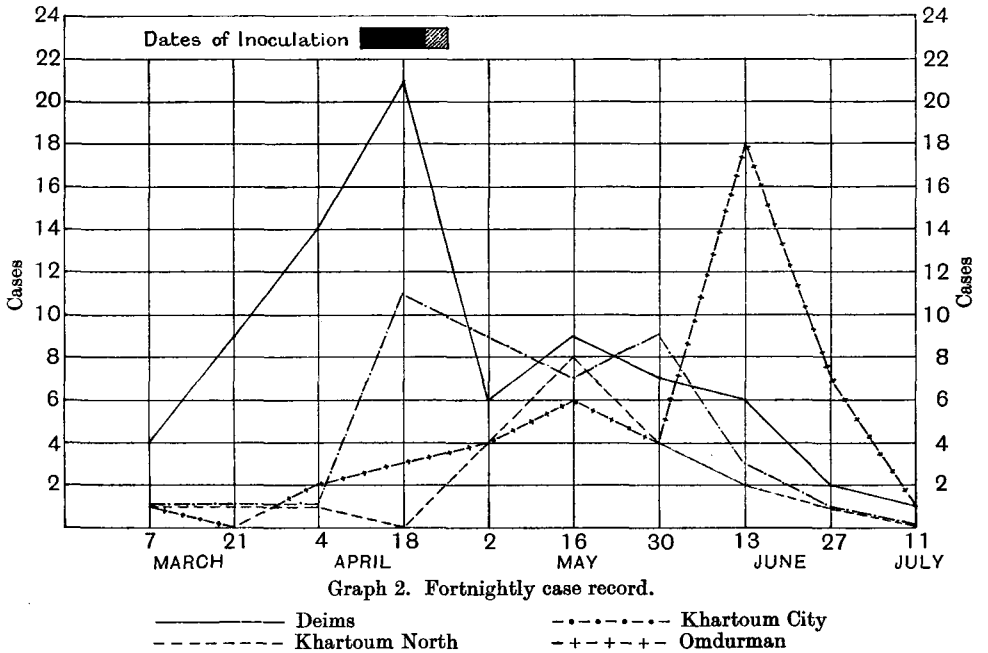
Graph 2 illustrates the epidemic as it affected Deims, Khartoum City, Khartoum North, and Omdurman, the four areas to be considered in the experimental observations.



Graph 2. Fortnightly case record.

Table II shows the case records when analysed by sex and age, and indicates that the morbidity rate was much smaller in the adult females than in the adult males.

Table II. *Analysis by sex and age.*

Group	Cases	Deaths	Case mortality %	Estimated number in population
Female infants in arms	5	2	—	87,000
Male infants in arms	8	7	—	
Female children	19	11	57·3	
Male children	70	41	58·5	
Female adults	24	19	79·1	101,500
Male adults	92	65	70·6	77,700
Totals	218	145	66·5	266,200

THE EXPERIMENT IN PROPHYLACTIC VACCINATION.

The experiment in prophylactic vaccination was carried out by inoculating 10,691 subjects with meningococcal vaccine (vaccine A), 10,451 subjects with T.A.B. vaccine (vaccine B) and leaving the remaining 245,058 natives uninoculated.

By inoculating alternate subjects with either vaccine A or vaccine B, and keeping the age and sex distribution as even as possible in the two groups, the necessities for valid statistical inferences were observed. The two groups were

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in all material respects alike, the effective exposure to the disease was identical, and it was hoped that by taking so large a number of subjects, a sufficient number of observations would be made, from which accurate conclusions could be drawn.

The possibility of the inoculations producing a negative phase, and so exposing the inoculated to an increased risk of infection was considered. The probable transient nature of the negative phase, however, led us to hope that, from the point of view of prophylaxis, it could be disregarded.

The vaccines.

Nine strains of the meningococcus were selected for the preparation of vaccine A, seven of these having been isolated from the early cases in the epidemic and two from Gedaref and Wad Medani 12 months previously.

All nine strains were later proved to be type II meningococcus, which organism apparently was the sole cause of the epidemic.

The medium used throughout for the isolation of the meningococcus, its maintenance in subculture, and the preparation of the vaccine, consisted of Loeffler's inspissated blood serum to which 1 per cent. glucose and 1 per cent. starch had been added.

In order to ensure suitable moisture conditions, a large surface for growth, and a strong culture of the meningococcus for vaccine preparation, the serum mixture was inspissated in large oblong bottles (Johnnie Walker Whisky bottles as made for export) so as to form a layer some $\frac{1}{4}$ in. thick on three of the four sides.

Twenty-four hour subcultures of the various strains of meningococcus were alone used for seeding the culture bottles, which were subjected to incubation at 37° C. for 24 hours, the creamy surface growth being then scraped off, and suspended in 0·5 per cent. phenol in normal saline.

The suspensions of the various strains, after standardising at 2000 million organisms per 1·0 c.c., were pooled in equal proportions to form the vaccine, which was then subjected to incubation at 37° C. for 6 hours to allow of autolysis of the meningococci with the liberation of endotoxin. After testing for sterility, the vaccine was used for inoculation, all the vaccine being used up within 1 week of preparation.

The control T.A.B. vaccine (vaccine B) was the stock vaccine as prepared in the Wellcome Tropical Research Laboratories, diluted to contain 200 million typhoid, 100 million paratyphoid A and 100 million paratyphoid B organisms per 1·0 c.c. This vaccine was used as the control, because, firstly it produced a reaction in the inoculated clinically similar to that of the meningococcal vaccine, and secondly its general appearance gave rise to no suspicions in the minds of inoculated or inoculators that two dissimilar vaccines were being used. Moreover, T.A.B. vaccine was used rather than normal saline, as in some measure it justified the subjection of so many people to the dangers attendant on inoculation.

THE INOCULATION CAMPAIGN.

Inoculation was carried out in Deims between April 11th and 22nd, in the Gordon College, Khartoum City, on April 13th, in Khartoum City between April 22nd and 25th, and in Khartoum North on May 16th.

Two inoculating teams, each team consisting of an inoculator, a record keeper, a marker, and an iodine dabber, all natives of the Sudan, worked at two tables in the same tent, one team giving vaccine A and the other vaccine B.

Native police lined up the subjects for inoculation and maintained order, while a British Sanitary Inspector superintended the whole procedure.

Each person received either 1·0 c.c. of vaccine A or of vaccine B, intramuscularly in the upper arm, and was marked accordingly.

Those inoculated with vaccine A received three longitudinal streaks with a silver nitrate stick on the moistened left thumb nail, which served to distinguish them from those inoculated with vaccine B, who received three similar streaks on the right thumb nail. This proved to be an excellent method of identification, as the streaking was still plainly visible at the end of 100 days.

The inoculating teams remained in absolute ignorance of the true nature of the two vaccines throughout the experiment, as did also the sanitary staff and the medical staff of the hospitals, who had to deal with cases of the disease arising among the inoculated.

The meningococcal vaccine produced some slight malaise with fever for 48 hours, which was then followed by a feeling of well-being. Some of the natives asked for a second dose of vaccine, as they said it "made them strong," but this was refused.

No untoward results directly attributable to the administration of the vaccine occurred.

Table III shows the numbers of the inoculated.

Table III. *Total number of inoculations.*

Vaccine A = 10,691; Vaccine B = 10,451.

		Deims		Gordon College		Khartoum City		Khartoum North Prison		Khartoum City Prison	
		A	B	A	B	A	B	A	B	A	B
Infants in arms	Male	227	278	0	0	15	13	0	0	0	0
	Female	230	268	0	0	11	12	0	0	0	0
Children	Male	696	615	347	320	522	603	38	34	8	0
	Female	475	462	0	0	44	150	40	15	0	0
Adults	Male	3371	3234	0	0	1861	1657	301	359	92	0
	Female	2130	2056	0	0	131	372	106	3	46	0

THE RESULTS.

The actual figures for the number of cases of, and deaths from, meningococcal meningitis among the uninoculated and the inoculated, before and after the commencement of prophylactic vaccination are tabulated in Table IV. Corrected figures are also shown in this table, as certain of the subjects in both inoculated groups died from the disease within 24 hours after inoculation.

Table IV. *Cases and deaths occurring among the inoculated and the uninoculated before and after the commencement of inoculation. Actual figures.*

	Population at risk	Cases occurring before inoculation commenced		Cases occurring in uninoculated after commencement of inoculation			Inoculations: Vaccine A					Inoculations: Vaccine B				
								Total		Corrected			Total		Corrected	
		Cases	Deaths	Number	Cases	Deaths	Number	Cases	Deaths	Cases	Deaths	Number	Cases	Deaths	Cases	Deaths
Deims	17,000	53	30	2958	2	2	7129	13	10	7	5	6913	11	7	7	5
Khartoum City	10,200	16	9	4809	22	14	2584	0	0	0	0	2807	5	3	3	2
Omdurman	137,000	48	36				No inoculations done									
Khartoum North Prison	878	9	8	—	—	—	485	2	0	2	0	393	3	1	3	1
Totals	165,078	126	83	7767	24	16	10,198	15	10	9	5	10,113	19	11	13	8

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Table V. *Results of inoculation in Deims and Khartoum City.*

Estimated population = 27,000.
Cases developing the disease within 24 hours of inoculation are excluded.

		Vaccine A			Vaccine B		
		Inoculations	Cases	Deaths	Inoculations	Cases	Deaths
Infants in arms	Female	241	0	0	280	0	0
	Male	242	1	1	291	1	1
Children	Female	519	1	0	612	0	0
	Male	1218	3	2	1218	1	0
Adults	Female	2261	1	1	2428	3	3
	Male	5232	1	1	4891	5	3
Totals		9713	7	5	9720	10	7

The number of cases in each group is very small, therefore the findings in Deims and Khartoum City, the largest groups, will alone be discussed.

The period of maximum incidence of the disease had been passed in Deims before inoculation was completed, while inoculation was completed in Khartoum City before this period was reached. This is demonstrated in Table VII which shows the weekly cases for Deims and Khartoum City and the dates of inoculation.

Table V shows the corrected figures in the various age and sex groups among the inoculated, while Table VI gives the figures per 1000 individuals in the various groups, in Deims and Khartoum City.

In Khartoum City no cases or deaths from meningococcal meningitis occurred among the subjects inoculated with the meningococcal vaccine (vaccine A), while there were 1·06 cases and 0·71 deaths per 1000 from the disease, among those inoculated with the T.A.B. vaccine (vaccine B); a result apparently favourable to the use of vaccine A as a prophylactic. When the figures are subjected to statistical analysis, however, it is found that the standard deviation is 1·731, and the difference between the number of cases in the two groups is less than twice the standard deviation, giving odds against the result being due to errors of sampling of less than 22 to 1. The absence of significance in this finding is supported by the result in Deims, where there were 0·98 cases and 0·70 deaths per 1000 in the vaccine A group and 1·01 cases and 0·72 deaths per 1000 in the vaccine B group, that is no appreciable difference between the two groups.

CONCLUSION.

The use of a prophylactic vaccine, applied under strictly experimental conditions in an epidemic of meningococcal meningitis, proved ineffective as a means of combating the disease.

SUMMARY.

1. An epidemic of meningococcal meningitis, due to Type II meningococcus, occurring in a large native population is briefly described.

Table VI. *Cases and deaths per* 1000 *population.*

	Before commencement of inoculation		Uninoculated after commencement of inoculation		Vaccine A				Vaccine B			
					Total		Corrected		Total		Corrected	
	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
Deims	3·11	1·76	0·67	0·67	1·82	1·40	0·98	0·70	1·59	1·01	1·01	0·72
Khartoum City	1·56	0·88	4·57	2·91	0·0	0·0	0·0	0·0	1·78	1·06	1·06	0·71

Table VII. *Weekly case records for Deims and Khartoum City showing date of inoculations.*

	Feb.	March				April				May					June				July		
Date...	28	7	14	21	28	4	11	18	25	2	9	16	23	30	6	13	20	27	4	11	18
Deims	1	3	2	7	8	6	15	6	5	1	4	5	3	4	4	2	2	0	0	1	0
Inoculation, Deims	—	—	—	—	—	—	11	—	22	—	—	—	—	—	—	—	—	—	—	—	—
Khartoum City	1	0	0	1	0	1	6	5	2	7	1	6	4	5	2	1	1	0	0	0	0
Inoculations, Khartoum City	—	—	—	—	—	—	—	—	22	25	—	—	—	—	—	—	—	—	—	—	—

2. A method of preparing prophylactic meningococcal vaccine on a large scale, and its experimental application in the epidemic is demonstrated.

3. The results obtained in two similar groups of natives, one inoculated with meningococcal vaccine and the other with T.A.B. vaccine, as to the incidence of, and death rate from, meningococcal meningitis are detailed.

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