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Sulphadiazine-resistant group A meningococci isolated during the 1968 meningitis epidemic in Greece

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INTRODUCTION

Since Millar *et al.* (1963) have reported the occurrence of sulphadiazine-resistance in a group B strain of *Neisseria meningitidis* at the U.S. Naval Training Center in San Diego, several authors have reported the increasing prevalence of sulphadiazine-resistant group B and group C meningococci in the military and civil population (Bories, Faucon, Audiffren & Bonzom, 1964; Bories, Faucon, Oddou & Audiffren, 1965; Leedom *et al.* 1965; Bristow, van Peenen & Volk, 1965; Eickhoff & Finland 1965; Feldman, 1966; Farrell & Dahl, 1966; Dowd *et al.* 1966; Sanders, 1967; and others). In fact, group B meningococci were reported to be less uniformly inhibited by sulphonamides than other meningococcal types by Branham, as early as 1940 and 1953 (cited by Leedom *et al.* 1965). Love & Finland (1954) also had detected, among 50 group B strains isolated before May 1954, 24 % highly resistant to sulphadiazine. However, the San Diego epidemic was the first large-scale outbreak due to highly resistant strains.

Such striking observations of sulpha-resistance were not reported in group A strains of *N. meningitidis*. Yet Bories *et al.* (1964), among 83 strains of group A meningococci tested, found one which was resistant *in vitro* to a concentration of 5 mg./100 ml. of sulphadiazine and also four others to 1 mg./100 ml. Moreover R. Faucon (personal communication), observed sulphadiazine-resistance in group A strains isolated in 1967 in Morocco and in 1968 in Tchad.

In Greece little was known about the prevailing serological groups and the sensitivity to sulphonamides of the meningococci responsible for the disease until the end of 1967. In this country, meningococcal meningitis occurs in endemic form, with an epidemic wave usually every 8–10 years. Some of the epidemiological features of the disease in the last years are shown in Tables 1 and 2 and in Fig. 1. (Data from the Archives of the Public Health Division, Ministry of Social Welfare, and from Publications of the Population Department of the National Statistical Service of Greece.)

It can be seen from Table 1 that the morbidity rate per 100,000 inhabitants fluctuates between 9·41 (1954) and 1·66 (1962). The decrease in morbidity in the last ten years may be partly attributed to the larger use of chemotherapeutic agents by the physicians.

The case mortality rate in the last 9 years shows a fluctuation between 3·46 in 1959 and 9 in 1961.

The seasonal distribution of the disease for the periods 1961–3, 1964–6 and for

the year 1967 is shown in Table 2 and in Fig. 1. It can be seen that, except for the period 1961–3, the disease follows the usual seasonal pattern; that is to say, a big rise of the curve during the spring with a peak in March. This seasonal form is more evident for the year 1967. A similar seasonal incidence of meningococcal meningitis is reported by Taylor & Knowelden (1957), Wilson & Miles (1964), Bevan-Jones & Miller (1967) and others. The influence of the season may probably be due to environmental conditions, which create specific microclimatic influences in some population groups (army barracks, schools, etc.).

Table 1. *Morbidity and case mortality rate of cerebrospinal fever during the years* 1950–67* (*case fatality rate for the years* 1959–67)

Years	No. of cases	Morbidity per 100,000	Years	No. of cases	Morbidity per 100,000	Case mortality rate (%)
1950	587	7·76	1959	433	5·24	3·46
1951	499	6·52	1960	240	2·88	5·83
1952	493	6·37	1961	200	2·38	9·00
1953	331	4·23	1962	140	1·66	7·86
1954	743	9·41	1963	161	1·90	3·73
1955	308	3·87	1964	166	1·95	6·67
1956	389	4·84	1965	215	2·51	5·55
1957	318	3·93	1966	198	2·30	3·53
1958	392	4·80	1967	374	4·33	5·08

* For 1968 see text.

Table 2. *Seasonal swing in morbidity of cerebrospinal fever in Greece during the years* 1961–3, 1964–6 *and* 1967

Months	1961–3	1964–6	1967
January	13·37	7·60	6·68
February	10·98	12·44	10·43
March	11·38	15·37	17·91
April	10·57	12·26	12·04
May	6·99	10·36	15·24
June	9·78	10·54	9·09
July	4·79	7·08	6·15
August	3·79	4·66	5·61
September	5·59	2·94	5·08
October	8·98	3·63	3·21
November	6·59	5·69	4·55
December	7·19	7·43	4·01
	100·00	100·00	100·00
Total cases	501	579	374

Following the endemo-epidemic rise of 1967, a severe and extensive epidemic of meningococcal meningitis developed during the winter and the spring of 1968. Thus from January to April 1968, 716 cases were notified (January 57 cases, February 266, March 231, April 162). This number is about twice the number of

cases which occurred throughout 1967.* The cases during the 1968 epidemic occurred in most regions of the country, especially in army and navy barracks and to a lesser extent in schools and in other civil population. Moreover, an increase in the case mortality rate was noted in 1967 and 1968. This rate was 5·08 % in 1967 and 4·33 % from January to April 1968. The high increase in the morbidity rate and the rise in the case mortality rate may be explained by the probable emergence, in the population, of more virulent strains. This assumption, without excluding an eventual change in the susceptibility of the host, is corroborated by the fact that in the last few years, in some countries of Europe, Africa and Oceania, an increasing incidence of the disease has been observed (*Epidemiological and Vital Statistics Reports*, WHO, 1960, 1962–1967).

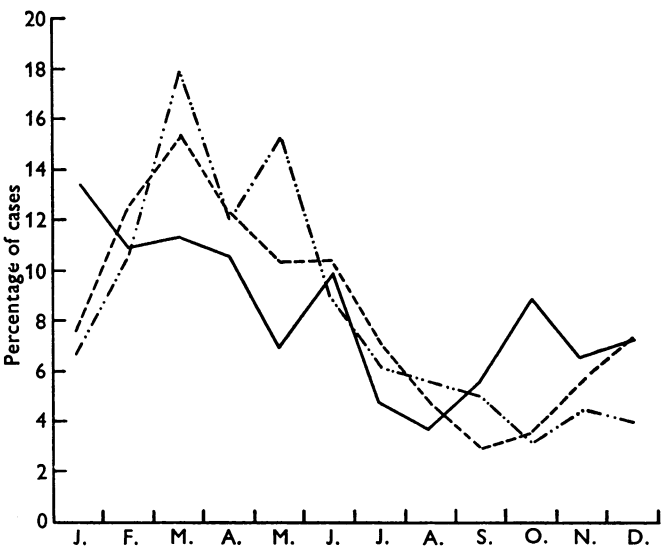

Fig. 1. Seasonal swing in morbidity of meningococcal meningitis in Greece during the years 1961–3 (——), 1964–6 (— —) and 1967 (—·· —··)

During the 1968 epidemic, we had the opportunity to isolate meningococci from patients and from healthy nasopharyngeal carriers and to determine their serological group and their susceptibility to sulphadiazine.

METHODS AND MATERIALS

Isolation media

For the detection of healthy carriers, nasopharyngeal swabs were taken and immediately streaked on Thayer–Martin selective medium (Thayer, Frank & Martin, 1965). This medium was prepared with Mueller–Hinton starch agar (Difco) to which supplement B (Difco), ristocetin (Abbott) and polymyxin B (Pfizer)

* Before this paper went to press the figures for the rest of 1968 became available. The total number of meningitis cases for the year was 1065, just over three times the annual average over the 18 years 1950–67, and nearly 50 % higher than the highest single annual total (743 in 1954.) Approximately two-thirds of these cases occurred between January and April, and one-third during the remaining eight months. The morbidity rate per 100,000 for the whole year was 12·09, and the case mortality rate was 4·03 %.

were added. The inoculated plates were incubated at 37° C. for 24–48 hr. under increased carbon dioxide tension (candle jar).

From clinical cases of meningitis the organisms were isolated by culturing the spinal fluid on chocolate agar.

Identification

The identification was based on conventional characters. Meningococci were Gram-negative, oxidase-positive, fermented dextrose and maltose but not sucrose, and failed to grow on nutrient agar (Difco) at 37° C. and on tryptose agar (Difco) at 22–25° C. after prolonged incubation. All strains were serologically identified by the slide agglutination method with group-specific meningococcal sera. Serial tube agglutination tests were done only on eight strains which gave uncertain results by the slide technique (probably of group B).

Tests for sulphadiazine susceptibility

The *in vitro* testing of the susceptibility to sulphadiazine was performed by the plate dilution method on Mueller–Hinton agar (Difco). The range of sodium sulphadiazine concentrations incorporated in the medium was 0·1, 1, 5, 10 and 20 mg./100 ml. Sodium sulphadiazine solution in ampoules for intravenous injection (Maizel Lab. Inc.) was employed for this purpose. Two inocula from each strain were used. They were prepared as follows: The strains were grown at least twice for 18–24 hr. on Mueller–Hinton agar. From the last growth on this agar a slightly opalescent suspension of organisms in Mueller–Hinton broth was prepared. From this suspension a 1/10 dilution, again in Mueller–Hinton broth, was also prepared.* Inocula from both suspensions from each strain (undiluted and diluted 1/10) were streaked with a 4 mm. loop over 1 or 2 cm.^{2} of the surface of the sulphadiazine-containing plates. The plates were read after 24 and 48 hours. For this reading, use was made of the series of plates streaked with the inoculum which showed on the control plate, after 24–48 hr, an almost confluent layer of bacterial growth. These *in vitro* tests were repeated once more on strains of reduced sensitivity. In addition, we compared the method we used for the determination of sulphadiazine susceptibility with the technique used for the same purpose by Bories *et al.* (1964) in the International Reference Centre for meningococci. Their method differs from ours in that they use pure sulphadiazine which they dissolve in 0·1 N-NaOH, and in their inoculating the plates from a 4 hr. growth in Mueller–Hinton broth. The results of sulphadiazine susceptibility by both these methods on 9 group A and 1 group B meningococci were in general agreement.

Source of strains

A total of 105 strains of *N. meningitidis* were examined. They were isolated from the following sources:

(1) *From patients*

Twenty strains from the spinal fluid of patients were examined. Of these, ten

* Mueller–Hinton broth was prepared by soaking in water, Mueller–Hinton starch agar (Difco) for 1–2 hr. and by decanting the supernatant.

were isolated from cases which occurred in soldiers in army barracks situated in five different regions of the country and the remaining ten were from civilians, also from various areas of Greece. These isolations were done between January and April 1968, except for one in June 1968.

(2) *From nasopharyngeal carriers*

(a) *Army barracks.* Nasopharyngeal swabs were taken, on 21 February 1968, from 50 healthy soldiers of an army barracks in the region of Attica. In this barracks four cases of meningitis occurred between 29 December 1967, and mid-February 1968. The strains of three out of the four cases were examined and found to belong to serological group A.

One gramme of oral sulphadiazine, twice daily for 3 days, had been given to all the men of the barracks on three occasions. These were the dates on which each of the first three cases (i.e. 29 December 1967, 21 January and 8 February 1968) appeared. Prophylactic antibiotics had not been given.

After the last administration (8–10 February) of the sulphadiazine, 50–60 privates, who were on leave, returned to the barracks.

(b) *Naval Training Centre.* Swabs were taken on 14 March 1968 from 54 healthy recruits of a Naval Training Centre which is also in the Attica area but about 10 miles away from the army barracks already referred to. This centre consists of two communicating training centres, one of which had a population of 896 and the other one of 779 persons. Thus, the sample taken represented about 3 % of the total population. Two-thirds of the total naval personnel were new recruits. The last recruits joined the centre on 7 January 1968. At the beginning of January a high proportion of cases of pharyngitis was noted.

In this centre, 11 cases of meningitis appeared between 23 January and 11 February 1968. All cases, except one, occurred among recruits. It is worth noting that in one of these training centres, which has five wards, four out of the five cases occurred in one ward.

On 23 January 1968 all the individuals of the centre were placed on prophylactic sulphonamides. They were given oral sulphadiazine 3 g. daily for about 6 days and thereafter 1 g. of sulphamethoxypyridazine daily, until 6 February 1968. After a 3–day interruption, sulphamethoxypyridazine was once again ordered for 3 more days.

No antibiotics had been used for prophylactic purposes in this centre.

(c) *Civilians.* Nasopharyngeal samples were taken from 51 healthy civilians on 6 March 1968. Out of these, 36 were students of the sanitarian branch of the Athens School of Hygiene and 15 were employees of the Athens Health Centre. No case of clinical meningitis had occurred among the contacts of these persons. Their homes were scattered in almost all parts of Athens. Sulphonamides or antibiotics had not been taken by any of them during the months preceding their examination.

RESULTS

Strains isolated

A total of 105 meningococcal strains were isolated from patients and from healthy nasopharyngeal carriers.

The number and the percentage of the strains of different serological groups isolated from various sources are analysed in Table 3.

In addition to the results shown in Table 3, the following data can be inferred from the reading of this table. Of the total number of 105 strains isolated, 66 belong to group A, 36 to group B and 3 to group C. Two of these meningococci, one of group A and one of group B, were harboured by the same healthy carrier. In the army barracks a total of 72 % healthy carriers of various groups of meningococci was found, while in the Naval Training Centre this rate was 59 %. Among civilians 31 % were carriers of only group B meningococci.

Table 3. *Numbers and groups of meningococci isolated from healthy carriers and patients*

(Figures in parentheses indicate percentages.)

Meningococcus groups isolated	Carriers*			Patients†	Total
	Soldiers	Sailors	Civilians		
Group A	26 (52)	21 (39)	0	18 (90)	65 (37)
Group B	6 (12)	11 (20)	16 (31)	2 (10)	35 (20)
Group C	3 (6)	0	0	0	3 (2)
Mixed A+B	1 (2)	0	0	0	1
Negative	14 (28)	22 (41)	35 (69)	0	71 (41)
Total examined	50	54	51	20	175

* From different areas of Attica. † From different regions of the country.

It is to be mentioned that all the ten cases of meningitis among soldiers were group A infections, while out of the ten civilian cases, eight were group A and two were group B infection.

Eight strains which gave equivocal results in the serological grouping were sent to the International Reference Centre at Marseille for examination. They were all found to belong to group B. In addition, for control purposes, eight group A and three group B meningococci, taken at random, were also sent to this Centre. Our typing on these 11 strains was confirmed.

Susceptibility to sulphadiazine

The susceptibility of 101 of the meningococci (four strains were lost) to sulphadiazine, tabulated according to their serological group and their origin, is shown in Table 4. The sulpha-susceptibility of eight group A and 11 group B meningococci, taken at random, was also examined by Dr R. Faucon, Director of the International Reference Centre for meningococci. Differences in susceptibility were found in

some strains. However, of the eight group A strains which were sent to this Centre, Dr Faucon found one resistant to 20 mg./100 ml. of sulphadiazine, another to 5 mg./100 ml. and four to 1 mg./100 ml.

It is of interest to note that Dr Faucon has also tested, by the disk technique, the susceptibility of these 19 strains to penicillin, streptomycin and chloramphenicol. They were all found to be sensitive to these antibiotics.

Table 4. *Susceptibility of strains of meningococci to sulphadiazine*

(Figures in parentheses indicate percentages.)

Origin of strains	Number of strains showing minimum inhibitory concentration of (mg./100 ml.): 0·1	1	5	10	20	>20	Total no. of strains
			Group A strains				
Soldiers*	1 (4)	0	16 (59)	10 (37)	0	0	27
Sailors*	0	0	2 (10)	10 (53)	6 (32)	1 (5)	19
Patients	0	1 (6)	9 (50)	4 (22)	2 (11)	2 (11)	18
Total group A	1 (1½)	1 (1½)	27 (42)	24 (37)	8 (12)	3 (5)	64
			Group B strains				
Soldiers*	5 (71)	1 (14)	0	1 (14)	0	0	7
Sailors*	0	1 (9)	2 (18)	5 (45)	3 (27)	0	11
Civilians*	12 (86)	0	2 (14)	0	0	0	14
Patients	0	1	0	0	0	1	2
Total group B	17 (50)	3 (9)	4 (12)	6 (18)	3 (9)	1 (3)	34
			Group C strains				
Soldiers*	2	1	0	0	0	0	3

* Carriers only

DISCUSSION

The high proportion of group A meningococci (90%) isolated from patients during the 1968 epidemic of meningococcal meningitis points to the fact that organisms of this serological group were responsible for this epidemic.

An important aspect of our study is the isolation of group A meningococci resistant or of reduced sensitivity to sulphadiazine (see Table 4). These organisms came from different regions of the country. Three strains out of 64 were resistant to a concentration of 20 mg./100 ml.; two were isolated from patients of different regions and one from a healthy carrier. Two strains only were sensitive to concentrations of 0·1 mg./100ml. and 1 mg./100 ml., respectively. The minimal inhibitory concentrations of sulphadiazine for the remaining strains were as follows: 5 mg./100 ml., 27 strains; 10 mg./100 ml., 24 strains; 20 mg./100 ml., 8 strains.

Table 4 shows clearly that the group A meningococci isolated from carriers of the Naval Training Centre (naval recruits) were on the average more resistant to sulphadiazine than those isolated from carriers of the army barracks. This is probably due to the fact that persons in the Naval Centre had received larger and

more prolonged doses of sulphonamides and as a result more resistant mutants were selected in this centre.

The finding of *in vitro* resistance to sulphadiazine in group A meningococci isolated from individuals of the army barracks and of the Naval Training Centre is corroborated by the detection of high rates of group A healthy carriers in both military establishments, 52 % and 38·9 % respectively, despite the fact that all individuals in both establishments had been placed under chemoprophylaxis shortly before the samples were taken. In the army barracks, three standard prophylactic courses of sulphadiazine had been given (the last course was terminated 11 days before the samples were taken). In the Naval Training Centre large and prolonged doses of sulphadiazine and sulphamethoxypyridazine had been given $4\frac{1}{2}$ weeks before the nasopharyngeal swabs were taken.

Moreover, in both establishments several cases of meningitis appeared during, or shortly after, the chemoprophylaxis. The strains from three of these patients were examined and were found to belong to group A. They were also found of reduced sensitivity to sulphadiazine (minimal inhibitory concentration of 50 mg./100 ml.). In addition, sulpha-resistant group A meningococci with minimal inhibitory concentrations to sulphadiazine ranging from 50 mg./100 ml. to more than 200 mg./100 ml., were isolated from patients belonging to other army barracks, in which swabbing for healthy carriers was not done, but in which repeated courses of chemoprophylaxis had been administered before the appearance of the clinical cases. We may assume from these observations that group A meningococci, resistant to prophylactic doses of sulphonamides, were prevalent in these military establishments.

As a matter of fact, according to data accumulated by the U.S. army and quoted by Brown & Condit in 1965 (cited by Leedom *et al.* 1965), strains resistant to 0·1 mg./100 ml. of sulphadiazine or more cannot be eradicated from the nasopharynx of carriers with standard doses of this drug. Therefore, from the results of our *in vitro* tests which showed that all the group A meningococci, except one, were strains with minimal inhibitory concentrations of 1 mg./100 ml. or more, we may assume that they could be classified as sulpha-resistant on epidemiological grounds. On the other hand, in patients, on account of the concentration of sulpha-drugs attainable in the blood and spinal fluid without excessive toxicity, many of these strains could eventually be sensitive on clinical grounds. However, those with minimal inhibitory concentrations of more than 5 mg./100 ml. could be expected to be clinically resistant.

Concerning the civilians examined, it is worth noting that none of the 51 healthy individuals swabbed was a carrier of group A meningococci, whilst of the 10 cases of meningitis in civilians, eight were group A infections (80 %) and only two group B. Although the healthy group of civilians examined was a very small one and came only from the Athens area, the absence of group A carriers among them, in contrast to the frequency of group A infection in civilian patients, seems to suggest that the responsible strains in the case of meningitis in the civilian population originated from highly crowded military establishments, etc., in which a high carrier rate of group A meningococci was detected.

Group B meningococci were less prevalent than group A in all groups of individuals examined, with the exception of the healthy civilians who harboured only group B organisms.

The detection of a high proportion of sulpha-resistant group B meningococci in the Naval Training Centre is not surprising if we keep in mind that 'sulpha-prophylaxis' was undertaken repeatedly in this centre and that the occurrence of resistant group B strains has been well known since 1963 (see introduction).

In contrast to the Naval Centre, in the army barracks, in spite of previous chemoprophylaxis, six out of the seven group B and three group C meningococci recovered were strains with minimal inhibitory concentrations to sulphadiazine of 1 mg./100 ml. or less. It is likely that these sensitive strains were introduced in the army barracks during the period between the last administration of sulphadiazine and the sampling from the nasopharynx. In fact, 50–60 men returned to the barracks during this 11-day period. Another possible explanation is that not all the individuals in the barracks had taken sulphadiazine as prescribed by the physicians. However, the Medical Officers of the establishment consider this second possibility highly improbable.

SUMMARY

During the 1968 epidemic of meningococcal meningitis in Greece, 90 % of the meningococci recovered from the spinal fluid of patients belonged to serological group A. In one army barracks and in one Naval Training Centre, where cases occurred, a rate of 52 % and 38·9 % respectively of healthy nasopharyngeal carriers of group A meningococci was found, despite repeated courses of sulpha-prophylaxis given to all the population of these military establishments shortly before the swabs were taken.

The susceptibility to sulphadiazine of 64 group A meningococci isolated from patients in different regions of the country and from healthy carriers was tested *in vitro*. It was found that only one strain was sensitive to a concentration of 0·1 mg./100 ml. of sulphadiazine and another to 1 mg./100 ml. For the remaining strains, the minimal inhibitory concentrations of sulphadiazine ranged from 5 mg./100 ml. to more than 20 mg./100 ml.

Thirty-six strains of group B meningococci were isolated from 34 healthy carriers and from two patients. Some of these strains were resistant to sulphadiazine. Only three strains of group C meningococci were isolated from healthy nasopharyngeal carriers in one army barracks.

We wish to express our thanks to Dr R. Faucon, Director of the International Reference Centre for meningococci, for the valuable help he gave to us during our investigation, as well as for the supply of the group-specific agglutinating anti-meningococcal sera.

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ADDENDUM

After this paper was sent for publication we read a paper (Alexander, Sanborn, Cherriere, Crocker, Ewald & Kay, 1968, *Science, N.Y.* **161**, 1019) in which the authors report that, during a meningitis epidemic in Meknes, Morocco, due to group A meningococci, most of the strains isolated from patients were resistant to sulphadiazine.