Reid (1954). He pointed out that some of the control groups are not properly selected and some of the experiments would be unethical to carry out. This investigation was simple and free from dangers. Although the number of patients was small—only 15 patients in each group—I found out that methylpentynol is a useful adjunct in the management of asthmatic patients.

Summary

Difficulties in choosing the right hypnotic for asthmatic patients are emphasized with special reference to morphine.

A brief description of pharmacological action of methylpentynol is given.

A clinical trial was carried out with methylpentynol on 15 patients suffering from bronchial asthma whose sleep was disturbed by asthmatic attacks. A similar group of 15 patients received a placebo. The results of treatment are presented.

The value of methylpentynol as an adjunct in the management of bronchial asthma is discussed.

My thanks are due to Mr. K. McIver, chief group pharmacist, North Lonsdale Hospital, and his staff for co-operation in this clinical trial; and to Dr. A. P. B. Waind, consultant physician, for his criticism in preparing the paper. British Drug Houses Ltd. supplied the methylpentynol ("somnesin") and blank capsules.

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SICKLING PHENOMENON IN NORTHERN GREECE

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Recent investigations for sickling in Greece showed that the sickle-cell trait is not a rare finding. After the investigation by Makrycostas¹ of the first sickle-cell anaemia cases in people originating from an isolated village of the Sparta district, several cases of sickle-cell anaemia and trait were reported, affecting people from different districts of Greece.²⁻¹⁵ Choremis *et al.*^{10, 11} found a focus of sickling in Thebes, close to Athens; the frequency of the sickling phenomenon in this area is not known.

The Investigation

A few cases of sickle-cell anaemia in people originating from the Chalkidiki district of Northern Greece were reported by different writers.¹²⁻¹⁸ Several cases of sickle-cell anaemia admitted to our clinic from Chalkidiki gave us the opportunity for a wide and systematic investigation of the sickling phenomenon in Northern Greece, by examination of people of different origin living in this area.

The sodium bisulphite method was used because of its sure and rapid results and its simplicity (read after 30 minutes). We have several times repeated most of our exam-

inations, so that the findings can be looked upon as reliable. We examined mostly schoolchildren aged from 6 to 12 years, because we thought that they best represented a large number of the families of the area under investigation.

A total of 7,063 subjects were examined. Among these were 5,008 indigenous people from families who had lived in the villages for several centuries without mating with strangers, and 2,055 people of varied origin (254 natives speaking a Slav dialect, 208 refugees from Eastern Roumelia, 380 refugees from Eastern Thrace, 578 refugees from the Russo-Turkish border, 180 refugees from the Smyrna area, 163 Turks of Western Thrace, and 292 gypsies). In these 2,055 people the test was definitely negative except for two positive cases whose parents originated from Smyrna (Asia Minor).

A total of 37 villages of indigenous people were covered, in 22 of which some cases of sickling were found. In these 22 villages 3,583 persons were tested and 537 showed the sickling phenomenon. In the remaining 13 villages the investigation gave negative results. The highest incidence of sickling was found in the southern part of Chalkidiki district (Sithonia Peninsula). In the village of Sykia we tested 846 out of the 2,400 inhabitants and found 265 positive (31.3%). In the village of Parthenon the sickling rate was 32%, in St. Nicholas village 24%, in Nikiti 19%, and in Ormylia 18%. The incidence of sickling in the remaining part of Chalkidiki and generally in Northern Greece ranges from 2 to 14%, as is clearly seen on the map printed overleaf.

Incidence of Sickling in N. Greece

No.	Villages	No. Examined	Age in Years	Sickling Positive	%	Origin of People Examined
1	Sykia	846	1-76	265	31.3	Indigenous
2	Parthenon ..	153	5-12	49	32.0	"
3	Nikiti	143	5-13	27	19.0	"
4	St. Nicholas ..	101	2-12	24	24.0	"
5	Ormylia	103	5-12	18	18.0	"
6	Valta	196	1-60	25	12.8	"
7	Kallithea ..	90	6-12	8	8.8	"
8	Pazarakia ..	150	4-50	21	14.0	"
9	Furka	92	2-15	2	2.2	"
10	Kallandra ..	90	3-20	2	2.2	"
11	Polychronon ..	160	4-56	13	8.7	"
12	Kapsochora ..	96	6-11	1	1.0	"
13	Paliouri	160	2-80	16	10.0	"
14	Kassandrinon ..	46	6-12	0	—	"
15	Chanioti	62	5-30	0	—	"
16	St. Paraskevi ..	50	6-12	0	—	"
17	Nea Skioni ..	40	3-45	0	—	"
18	Stageira* ..	—	—	—	—	"
19	Epanomi	183	7-14	5	2.7	"
20	St. Prodromos ..	177	6-12	0	—	"
21	Zangliveri ..	172	2-14	0	—	"
22	Hortiatia ..	159	5-14	0	—	"
23	Xylopolis ..	90	2-60	0	—	"
24	Halastra	108	7-13	4	4.0	"
25	Klidi	67	7-14	4	6.0	"
26	Tsinaforon ..	151	3-17	14	9.2	"
27	Korifi	142	4-14	18	12.6	"
28	Loutros	102	7-18	6	6.0	"
29	Leptokaria ..	106	3-14	3	3.0	"
30	Fytia	150	4-13	0	—	"
31	Nigrita*	—	—	—	—	"
32	Aidonochorion ..	136	8-15	4	3.0	"
33	Paleokomi ..	100	5-27	6	6.0	"
34	Prosotsani ..	220	6-12	0	—	"
35	Gratini	86	1-60	0	—	"
36	Kosmion	76	4-13	0	—	"
37	Soufli	205	1-50	0	—	"
		5,008		535		
38	Vrahia	92	7-12	0	—	Slav. dialect
39	Kimina	162	8-14	0	—	"
40	Trikalla	168	7-14	0	—	Refugees, E. Roumelia
41	Vathylakos ..	162	7-13	0	—	Refugees, Smyrna
42	Neon Petritsi ..	238	7-40	0	—	" mixed
43	Fitoki-Flamburon	181	7-16	0	—	Gypsies, Christian
44	Stavropolis ..	108	1-30	2	—	Refugees, mixed
45	Lekani	160	3-45	0	—	" "
46	Kechrocamos ..	102	7-65	0	—	" "
47	Paranestion ..	86	2-70	0	—	" "
48	Komotini	143	4-8	0	—	Mixed people
49	Arisvi	82	6-12	0	—	Refugees, E. Thrace
50	Aratos	163	5-58	0	—	Turks, W. Thrace
51	Elafochori ..	97	2-14	0	—	Refugees, E. Thrace
52	Elafochori ..	111	3-38	0	—	Gypsies, Moslem
		7,063		537		

* Positive cases noted.

Origin of the Phenomenon

The question now arises, what is the origin of the sickling phenomenon and what is the reason for such a high incidence in Greece? Herrick¹⁶ found in 1910 the first case of sickle-cell anaemia in an American negro. Later, other investigators reported cases exclusively in negroes or in half-castes. This distribution of the phenomenon led different authors to the thought that sickling appeared only in negroes.

On the other hand, Mediterranean anaemia was not found in coloured people during the early days of the investigation.

These two facts led us to regard both diseases as exclusively racial—that is, sickling in negroes and Mediterranean anaemia in whites. But in recent years several indisputable cases of Mediterranean anaemia have been found in coloured people.¹⁷ Four cases were reported in negroes, and the trait was found in a large number of their relatives,^{18,19} also a combination of Mediterranean anaemia and C-haemoglobin.²⁰ On the other hand, 14 cases of Mediterranean anaemia and trait in their relatives were reported in Chinese people²¹⁻²⁹ and 26 cases in Thai people and half-castes.²⁹ Apart from the above-cited cases, other authors report five cases in Indian children,³⁰ one in an American Indian child,³¹ and cases in Egyptian children.³²⁻³³ We must therefore reconsider the thesis that these morbid conditions affect only one race.

The hypothesis that sickle-cell disease was an exclusive phenomenon of the negroes and the half-castes did not seem well founded, since Cooley and Lee³⁴ and other authors^{1,35-37} reported cases in white people in whom mixture with negroes could be excluded.

Introduction into Greece

Yet this trend of thought was evident in the attempts to explain the sickling phenomenon in the Mediterranean Basin, where, for geographical as well as for historical reasons, the presence of negro blood in the whites of this area was taken for granted. This was thought to be a satisfactory explanation of the sickling phenomenon in Greece, although historical sources (classic, Byzantine,³⁸ and more recent writers^{39,40}) admit no negro invasion of Greece apart from pirate raids executed mainly by Saracens, who are, as is well known, of Arabian origin (Spanish Arabs).

It is worth mentioning here that a recent investigation in Africa has disclosed that the incidence of sickling phenomenon in Arabian tribes is the lowest recorded in that continent (0-2%).⁴¹ Generally, it showed us that the distribution of sickling in Africa is very interesting. The highest rate occurs in Central Africa^{41,45-59} and diminishes towards the north^{41,50} and the south.⁴⁰⁻⁴⁵ This distribution is probably related to the way of living of the tribes exposing the gene (static or not) to intermarriage, environmental factors, etc.

The same factors exist probably in Chalkidiki, the area under investigation. This district was from ancient times up until now the theatre of frequent wars, which caused a pronounced reduction in the population and resulted in adverse living conditions and the formation of highly inbred, static groups of population.

It therefore seems reasonable to conclude that the sickling phenomenon in Greece, which appears in several areas among highly inbred groups, has a common cause—for example, mutation—and is an indigenous, local, and static condition of the inhabitants of those areas. We would mention here that some time ago we also developed a parallel view for the pathogenesis of Mediterranean anaemia.⁴²⁻⁴⁴

Choremis *et al.*¹¹ agree with this view of the pathogenesis of sickling phenomenon, stating that sickling in Greece may theoretically be attributed to mutation of the gene and to the influence of malnutrition and malaria and intermarriage among Greeks during the last few centuries.

From recent data at our disposal, however, we cannot agree that malaria is a factor responsible for sickling. These data are included in a paper to follow.

Relation of Malaria to Sickle-cell Trait

Possibly malaria is indirectly responsible for the wide distribution of sickling in some areas of Greece. Knowing the resistance of heterozygotes to malaria, and the fact that the area under consideration was in pre-war times a hyper-endemic area, we think that this disease, by eliminating healthy people, increased the frequency of sicklers and so helped the multiplication and perpetuation of the gene. This is a possible means by which malaria was acting to balance out counter-selection.

Map showing distribution of sickling in Northern Greece.

Sickling phenomenon can be regarded as a particular characteristic of any race which shows it in the absence of admixture with another race in which it exists. Its higher incidence around the Mediterranean could be accounted for by the suggestion that some races of the Mediterranean basin, with a few exceptions in other parts of the world, appear to be more prone to develop a mutation affecting their blood-forming tissue. At the same time some unknown geophysical and other factors, one of which may possibly be malaria, favour the high frequency of this mutation in these areas of the globe.

Conclusions

The sickling trait exists in Northern Greece, particularly in Chalkidiki, where in the Sithonia Peninsula the rate is 32%, in the neck of the same peninsula the rate is 18–24%, in the Kassandra Peninsula and in the plain of Salonika it reaches 14%, and at the foot of Pangaion Mountain it is 6%.

The sickling phenomenon is mainly observed among highly inbred groups of natives; it is an indigenous, local, and static condition of this area.

The sickling is due to a mutated gene. Its high frequency and manifestation in a given area can be accounted for by inter-marriage and the elimination of the influence of counter-selection by malaria.

Mediterranean and sickle-cell anaemias must not be regarded as exclusively racial diseases, since many cases have been observed (a) of Mediterranean anaemia among coloured people (negroes, Chinese, Thais, Egyptians, Indians, and American Indians), (b) of sickle-cell anaemia among white people in whom any admixture with negro blood must definitely be excluded.

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COMPATIBILITY OF SICKLING WITH MALARIA

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The appearance of severe hereditary anaemias in areas where malaria has been endemic for many centuries raises the question of how far malaria can be considered to be connected with the aetiology of these anaemias. We rejected such a connexion for Mediterranean anaemia¹⁻³ because we had never found malaria in our patients or their relatives. On the other hand, according to some authors the tentative treatment of this disease caused no improvement of the anaemia or any decline in the fever when this was present. Some trials of experimental transmission of malaria from patients suffering from Mediterranean anaemia into animals (*Macacus rhesus*, etc.) were unsuccessful.

Several writers have tried to correlate sickle-cell anaemia and trait with malaria. But recent clinical observations and experimental findings show little compatibility between these two morbid entities. Many workers in Africa, observing the low frequency of malaria in sicklers in contrast to non-sicklers, have concluded that sicklers are more resistant than non-sicklers because they are possibly protected by some unknown factor against attack by malaria parasites. They also think that abnormal red cells are less subject to parasitism than normal cells, and so children bearing the trait and living in malaria-stricken areas have a better chance of reaching adult life than children with normal blood.⁴⁻⁸

On the other hand, a different opinion was given by Edington⁹ and Moore *et al.*,¹⁰ who found in Africa (Gold Coast and Nairobi) the same incidence of malaria in sicklers as in non-sicklers. It is worth pointing out, however, that Edington counted 500 malarial parasites