TUBERCULIN SENSITIVITY IN KUWAITI SCHOOLS

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The occurrence of infection with tuberculosis—and consequently a positive tuberculin reaction—was accepted a generation ago as a normal event of childhood. With the more recent antituberculous campaigns, a large number of persons escaped infection in their childhood, and now there are large communities in which the majority of young adults have also escaped infection. The rates of tuberculin sensitivity in children were found to have fallen steadily in the last 50 years, especially in communities in which the mortality from tuberculosis has declined.

Kuwait, on the Persian Gulf, is a recently established community. It was formed less than three hundred years ago, mostly from Arabs and to a less extent Persians. It has always been a rural community. With the discovery of oil in the last few years, it started to acquire the characters of an urban community.

The number of inhabitants in Kuwait is under 230,000. Over 60% of these are "foreigners" arriving after the discovery of oil. The number of "indigenous" Kuwaitis is about 80,000. In the last few years Kuwait has shown a very marked progress in many aspects of modern civilization. There are 61 schools, 15,000 boy students and 10,000 girl students. Over 80% of the students are "indigenous" Kuwaitis and less than 20% are "foreigners."

Present Investigation

A total of 1,348 schoolboys and 652 schoolgirls were examined. All of them were indigenous Kuwaitis. They ranged in age from 5 to 15 years.

Method.—The intracutaneous Mantoux test was used. Injections of 0.1 ml., containing 0.0002 mg. of P.P.D.—that is, 10 I.U.—were given intracutaneously on the anterior surface of the left forearm. The results were read 72 hours later. A reaction was regarded as positive when there was an area of infiltration measuring 6 mm. or more in diameter. Erythema without infiltration was disregarded. The results are shown in Tables I and II.

TABLE I.—Percentage of Positive Reactors to 0.0002 mg. of P.P.D.

Years:	5	6	7	8	9	10	11	12	13	14	15	Mean
Males ..	12.8	13.2	13.8	15.4	19.2	20.2	26.6	30.6	35.5	46.1	58.3	21.2
Females ..	8.0	10.3	12.0	14.3	14.7	13.6	15.9	16.6	25.9	37.5	42.9	15.0
Total	10.6	12.4	13.4	15.0	16.0	17.4	22.2	25.4	31.0	44.1	54.8	19.2

TABLE II.—Percentage of Severe Reactions with Infiltration 20 mm. or More in Diameter

	M	F	Total
Severe reactions among total students examined	5.2	2.7	4.4
" " " positive cases	23.8	20.0	22.9

Discussion

The results of tuberculin surveys vary widely from place to place and from time to time. In Vienna, for example, in 1908, 95% of the population were positive tuberculin reactors at 12 years, while in some recent surveys in Australia the percentage did not exceed 1.9 at the same age. Variations in susceptibility to tuberculous infection in various persons or in various communities depend on many factors, notably the influence of race and heredity, undernourishment, industrialization, poverty, overcrowding, etc.

The results of the tuberculin test for Kuwaiti students show that the percentage of positive reactors is relatively low till the age of 10 years (17.4); then it gradually rises to 25.4 at the age of 12, after which it increases very rapidly to reach 54.8 at the age of 15 (Table I). The percentage of positive reactors is definitely higher in males than in females during the age period of 5 to 15 years.

In spite of the environmental and nutritional factors which favour the spread of tuberculous infection in Kuwait, the incidence of the infection seems to be relatively low. Habits such as using common cups for drinking-water or coffee, eating with the fingers, spitting on the ground, and kissing the nose as a sign of respect are prevalent, although education will have, and undoubtedly is having, a marked effect. Also there is much dust and a high humidity—exceeding 95% in many days of the summer. The Kuwaiti diet is mostly soup and boiled rice; eggs, milk, cheese, fresh fruits, and vegetables are scarce. The diet is definitely deficient in proteins, fats, and vitamins. In a medical examination of 500 Kuwaiti students, over 40% were found to have clinical evidence of vitamin-A deficiency, and 70% gave a history of a definite protein deficiency. Another important factor is the great number of immigrants into Kuwait in the last few years. Many of them are badly off workers—mostly coming from Persia—and are living under the worst conditions of dirt, poverty, overcrowding, and physical exhaustion. The extent of tuberculous infection in this group has not yet been studied.

In spite of the above-mentioned deleterious factors—which would undoubtedly facilitate the spread of tuberculous infection—the incidence of tuberculous disease in Kuwait can be regarded as low. In a survey done on 8,414 Kuwaiti students of 5 to 15 years of age, 0.39% of the boys, and 0.17% of the girls showed tuberculous lesions on mass miniature radiography. The percentage for the whole group was 0.24. This low incidence of tuberculosis in the presence of the above-mentioned factors seems paradoxical but may be due to the fact that overcrowding in bedrooms is uncommon. During hot weather, which prevails throughout the greater part of the year, the Kuwaitis have the habit of sleeping in open places—either on the roof or in the house-yard. The efficient medical service and the free treatment available in the last few years encourage most of the people to attend at the various clinics for routine examination. Cases of disease are thus spotted at an early stage and patients have a chance of a full and gratuitous treatment. Whether the racial factor has a role in this low incidence cannot be evaluated.

Table I shows that the percentage of positive reactors rises rapidly after the age of 12 years. The percentage of negative reactors is relatively high below that age. Therefore the tuberculin test can be of value in diagnosis, as regards the Kuwaiti students, only below the age of 12; and after that its diagnostic value rapidly diminishes.

Summary and Conclusion

A tuberculin survey on 2,000 Kuwaiti students was made, using 0.0002 mg. of P.P.D. intracutaneously.

The percentage of positive reactors was found to be relatively low, especially under the age of 12 years.

The percentage of positive reactors was higher in males than in females.

The tuberculin test may be of diagnostic value in Kuwaitis only below the age of 12 years.

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BEMEGRIDE ANALEPSIS

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The article by Dotevall and Herner (1957) has prompted us to summarize some recent pharmacological observations concerning the safe and widespread analeptic activity of bemegride to hypnotics both structurally related and unrelated to it.

Bemegride (β -methyl- β -ethylglutarimide) will wake mice from moderately deep acute hypnosis (ready response to pain, moderate depression of corneal reflex, sleeping time 60–80 minutes) due to such structurally related hypnotics as barbiturates (pentobarbitone), thiobarbiturates (thiopentone), glutarimides (glutethimide; "doriden" and others), diketopiperidines (methypyrone; "noludar"), diketotetrahydropyridines ("persedon"), diketothiazanes ("dolitrone"), diketothiazolidines (5:5-diethyl-2:4-diketothiazolidine), monoureides (carbromal and bromvaletone), and succinimides (5-methyl-5-phenylsuccinimide and others) (Shaw, Simon, Cass, Shulman, Anstee, and Nelson, 1954; Shulman, 1956; Somers, 1956; Frey, Hushahn, and Soehring, 1956; Kimura and Richards, 1957; Shulman and Laycock, 1957a, 1957b). It also antagonizes such structurally unrelated hypnotics as substituted acetamides (phenyl-diethylacetamide), saturated and unsaturated alcohols (chlorbutol, methylpentynol, "placidyl"), aldehydes (chloral hydrate), carbamates (urethane), cyclic ethers (paraldehyde), and sterols ("viadril") (Frey *et al.*, 1956; Kimura and Richards, 1957; Shulman and Laycock, 1957c). Its effect on deep acute hypnosis (minimal response to pain, marked depression of corneal reflex, frequent cyanosis and death, sleeping-time 2–12 hours) due to these drugs has been indicated by Kimura and Richards (1957) and Shulman and Laycock (1958). Further, bemegride will antagonize morphine-induced respiratory depression but not hypnosis or analgesia in the rabbit and dog (La Barre, 1957; La Barre, Dumont, and Desmarez, 1957; Shulman and Laycock, 1957c).

Clinical antagonism has been reported to such drugs as pentobarbitone, thiopentone, glutethimide, methypyrone, persedon, primidone, carbromal, and bromvaletone, either alone or occasionally combined with structurally unrelated hypnotics (Shulman, Shaw, Cass, and Whyte, 1955; Harris, 1955; Holten, 1956; Palmer, 1956; von Planta and Klingler, 1956; Dotevall and Herner, 1957).

A current quantitative investigation of this problem in mice (Shulman and Laycock, unpublished observations) indicates that at moderate levels of hypnosis the analeptic activity of bemegride to structurally related hypnotics is confined between much narrower limits than that shown to

structurally unrelated hypnotics. Bemegride is generally a more potent analeptic to this latter class of substance.

We wish to emphasize the high margin of safety associated with the administration of bemegride in the relief of moderate hypnosis induced by both classes of drugs. Significant reduction in sleeping-time ($p \leq 0.001$) has been obtained by the administration of mildly convulsant doses of bemegride (20 mg./kg. each 15 minutes) to mice narcotized with hypnotics of 15 structurally different types. A few transient and minimal signs of toxicity have been occasionally observed in the case of only two drugs (urethane and β -methyl- β -n-amyglutarimide).

The administration of convulsant doses of bemegride (60 mg./kg. stat. and up to 6 doses of 30 mg./kg. at seven-minute intervals) to mice deeply narcotized with the same series of structurally diverse hypnotics also resulted in a significant decrease in sleeping-time ($p \leq 0.001$) in the majority of cases (carbromal, chloral hydrate, 5:5-diethyl-2:4-diketothiazolidine, dolitrone, methypyrone, methylpentynol, paraldehyde, pentobarbitone, persedon, phenyl-diethylacetamide, placidyl, and viadril). Transient and mild signs of toxicity (tremors and Straub tail) followed awakening from such hypnosis due to chloral hydrate, 5:5-diethyl-2:4-diketothiazolidine, dolitrone, and phenyldiethylacetamide.

Antagonism was less pronounced and toxicity more marked in the case of deep hypnosis due to urethane, glutarimide, and succinimide. At slightly higher doses of these hypnotics bemegride treatment resulted in early antagonism (corneal reflex and response to pain), followed by respiratory depression and death preceded, in the case of urethane, by severe convulsions. This potentiation was greatest in the case of β -methyl- β -n-amyglutarimide, which, like bemegride, is a β , β -disubstituted glutarimide.

These results support the advisability of gradual titration of analeptic against hypnotic under strictly supervised conditions in an endeavour to keep the animal in the "safe state" (Shulman *et al.*, 1955).

Although great care should be exercised in too freely extrapolating the results of these laboratory investigations to the treatment of clinical cases, it is hoped that these observations may be helpful to the clinician faced with the diagnosis and treatment of the patient in coma, particularly where self or accidental administration of hypnotics may be suspected as the underlying cause. The careful intravenous administration of bemegride (up to three 50-mg. doses at intervals of 5 to 10 minutes) would appear to be a safe and useful diagnostic and possibly therapeutic aid, especially in the young patient in whom the likelihood of cerebrovascular accident may be anticipated to be minimal and preliminary investigation of whom has rendered the diagnosis of acute metabolic disturbance unlikely.

The value of bemegride in the diagnosis of an epileptiform focus has been previously indicated (Delay, Verdeaux, Verdeaux, Drossopoulo, Schuller, and Chanoit, 1956). Additional aspects of bemegride activity have been reviewed by Shaw (1957).

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