

# PHENOBARBITAL AND THE SHOULDER-HAND SYNDROME

BY

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Three cases of severe bilateral shoulder-hand syndrome were observed within a few months of each other, all three in patients who were being treated with phenobarbital because of epilepsy; one received phenytoin as well. In one of these cases the diagnosis of epilepsy became improbable; the electro-encephalogram revealed no signs of epilepsy, but rather of chronic barbiturate poisoning. A possible relationship between barbiturate treatment and the shoulder-hand syndrome was therefore investigated.

### Material and Methods

The case histories of all patients with shoulder-hand syndrome admitted to the Department of Rheumatology during the years 1954-64 were reviewed. The original diagnosis in each case was checked according to the following criteria: pain and/or stiffness of the shoulder; diffuse swelling or atrophy of the soft tissues of the homolateral hand. Patients with fractures or dislocations of the homolateral extremity and patients with joint disease other than mild osteo-arthritis were excluded. The shoulder-hand syndrome was regarded as bilateral if both hands showed dystrophic changes.

Two groups of patients, of the same number, matched for age and sex but otherwise unbiased, were used as controls: one group had scapulohumeral periarthritis and the other cervicobrachial neuralgia.

In all three groups other illnesses and medication prior to the onset of the presenting syndrome were ascertained.

### Results

75 cases of the shoulder-hand syndrome were available for analysis (Table I). In 29 cases both hands were affected. There was a slight preponderance of males. The ages ranged from 22 to 81 years, the majority were from the older age groups, 37 being over 60 years old.

TABLE I  
SEX, AGE, AND SITE OF LESION IN 75 PATIENTS WITH SHOULDER-HAND SYNDROME

Sex	Male	..	..	..	..	..	41
	Female	..	..	..	..	..	34
Age (yrs)	Mean	..	..	..	..	..	58.5
	Standard Deviation	..	..	..	..	..	±12.4
	Range	..	..	..	..	..	22-81
Site	Bilateral	..	..	..	..	..	29
	Unilateral	..	..	..	..	..	46

In 33 patients sedatives had been used before and during the development of the syndrome; this was the case with only eight of the 75 cases of scapulohumeral periarthritis and one of the 75 cases of cervicobrachial neuralgia (Table II). Phenobarbital could be identified as the drug used in 25 patients with the shoulder-hand syndrome and in two patients with scapulohumeral periarthritis. This difference between those with shoulder-hand syndrome and the two control groups appeared to be significant ( $P < 0.01$ ). On the other hand, no significant difference was found between the three groups in regard to other barbiturates, undefined sedatives, or other drugs.

TABLE II  
DRUGS USED BEFORE ONSET OF PRESENTING SYNDROME

Drug	Shoulder-hand Syndrome	Scapulohumeral Periarthritis	Cervicobrachial Neuralgia
Phenobarbital	25	2	-
Other barbiturates	2	1	-
Unspecified sedatives	6	5	1
Phenytoin	4	-	-
Isoniazid	4	-	-
Anticoagulants	2	3	1
Tranquillizers	2	-	2

A few drugs not mentioned were used only in a single instance.

In most of the patients suffering from shoulder-hand syndrome coincident with phenobarbital treatment involvement was bilateral (Table III). Nineteen of 29 patients with bilateral shoulder-hand syndrome were treated with phenobarbital, as against only six of 46 with unilateral involvement. This difference is significant ( $P < 0.01$ ).

TABLE III  
DRUGS USED BEFORE ONSET OF SHOULDER-HAND SYNDROME

Drug	Shoulder-hand Syndrome		
	Bilateral	Unilateral	Total
Phenobarbital	19	6	25
Unspecified sedatives	5	1	6
Phenytoin	4	—	4
Isoniazid	3	1	4

Of the ten patients with bilateral shoulder-hand syndrome who had not previously taken phenobarbital, five were using other sedatives, and three isoniazid.

The reasons for giving phenobarbital treatment varied widely (Table IV), but epilepsy proved to be the commonest. Nine cases of concurrent epilepsy and shoulder-hand syndrome were found, of which seven were bilateral. In only one of the patients with unilateral involvement had the diagnosis of epilepsy not been made before the onset of the shoulder-hand syndrome, but this patient had been treated for some years with phenobarbital for another reason, *viz.* epigastric pain. Epilepsy was the only condition found more commonly ( $P < 0.01$ ) in patients with the shoulder-hand syndrome than in the two control groups (in which it was absent).

TABLE IV  
INDICATIONS FOR PHENOBARBITAL TREATMENT, AND SITE OF LESION

Diagnosis	Shoulder-hand Syndrome	
	Bilateral	Unilateral
Epilepsy	7	1
Psychosis/neurosis	4	—
Pituitary tumour (operated)	1	—
Angina pectoris	—	1
Hypertension	—	1
Chronic bronchitis	2	—
Pneumonia	—	1
Menière's syndrome	2	—
Epigastric pain	—	1
Insomnia	2	—
Headache	1	—
Nervousness	—	1
Total	19	6

In sixteen of the 25 patients who had received phenobarbital before the shoulder-hand syndrome developed, the daily amount given could be traced: all had received 100 mg. or more (Table V). Doses

TABLE V  
DOSE AND DURATION OF PHENOBARBITAL TREATMENT, AND SITE OF LESION

Phenobarbital Therapy		Shoulder-hand Syndrome	
		Bilateral	Unilateral
Daily Dose (mg.)	100	4	—
	150	4	3
	200	2	—
	300	1	—
	Over 300	2	—
	Not known	6	3
Duration	Less than 4 wks	3	2
	1-11 mths	5	1
	1-10 yrs	4	3
	Over 10 yrs	5	—
	Not known	2	—

of more than 150 mg. a day were found in cases of bilateral involvement only. The duration of treatment before the onset of the shoulder-hand syndrome varied from a few weeks to more than 20 years (Table V). Treatment appeared to have gone on longer in cases of bilateral involvement than in unilateral cases.

With the exception of a predominance of bilateral involvement, no clear difference in the clinical picture of the shoulder-hand syndrome could be made out between those patients who had received previous phenobarbital treatment and those who had not. The acute symptoms of the shoulder-hand syndrome—burning pain, oedematous swelling, hyperhydrosis, etc.—had subsided within 6 months leaving no signs of atrophy or contracture in only five patients, all with unilateral involvement. These were the youngest in the whole group (ages varying between 22 and 41 years) and none had been treated with sedatives. In the other patients, including all those treated with phenobarbital, the hypertrophic stage lasting about 3 to 9 months was followed by atrophic changes of the hand(s) and contractures of the fingers of greater or lesser severity. Continuation of the phenobarbital treatment after the onset of the shoulder-hand syndrome did not appear to affect the prognosis.

### Discussion

In this series, one-third of all cases of the shoulder-hand syndrome occurred during phenobarbital treatment, with a striking preponderance of bilateral involvement. Some decades ago, in the French literature, attention was drawn to the occurrence of arthralgia, sometimes accompanied by contracture, during treatment with barbiturates, especially phenobarbital (Maillard and Renard, 1925; Maillard and Thomazi, 1931; Bériel and Barbier, 1934; Castin and Gardien, 1934). This condition, called

"rhumatisme barbiturique" or "rhumatisme généralisé", was encountered almost exclusively in older people treated for different conditions with barbiturates. As far as can be assessed from these papers, contractures were reported only in the shoulder, wrist and/or finger joints. Some cases, with a strong clinical resemblance to the shoulder-hand syndrome, were also described in the Scandinavian literature (Lövgren, 1948).

The shoulder-hand syndrome, sometimes accompanied by generalized joint pains, has recently been noted in patients treated with isoniazid for tuberculosis (Good, Green, and Zarafonitis, 1965; Dubra, Agüero, Chamoles, Marengo, and Epelbaum, 1965). In attributing a causative role to this drug, it is argued that it is known in experimental animals to cause neuropathy—perhaps by interfering with pyridoxine metabolism. As far as is known, no such effect of barbituric-acid derivatives has been described. While symptoms of the shoulder-hand syndrome during isoniazid treatment become usually manifest about 4 weeks after the onset of treatment, the duration of phenobarbital treatment before the onset of the shoulder-hand syndrome ranged from a few weeks to more than 10 years. It seems improbable, therefore, that phenobarbital plays a similar role to that of isoniazid in the pathogenesis.

Obviously there were widely divergent reasons for using phenobarbital in our patients. Nevertheless it might be contended that phenobarbital consumption is only a common denominator of subjects who are otherwise prone to develop the shoulder-hand syndrome. Thus it has been claimed that anxiety neurosis predisposes to this syndrome (Kahlmeter, 1930), and it can be imagined that in this type of patient sedatives are more readily prescribed. However, features of neurotic personality structure have also been demonstrated both in patients with scapulohumeral peri-arthritis and in those with cervicobrachial neuralgia, as compared with a healthy control group (Oesterreicher and van Dam, 1964). In patients with the former conditions, a significantly lower incidence of phenobarbital usage was found than in the group with the shoulder-hand syndrome.

The information presented therefore appears to indicate that phenobarbital might—by some mechanism as yet unknown—predispose to the occurrence of the shoulder-hand syndrome, although more direct evidence is still required.

#### Summary

A history of prior treatment with phenobarbital, of varying duration and dose, was found to be present

in nineteen out of 29 consecutive cases of bilateral shoulder-hand syndrome and in six out of 46 patients with unilateral involvement. A significantly lower incidence of phenobarbital consumption was found in two matched control groups comprising cases of scapulohumeral peri-arthritis and cervicobrachial neuralgia respectively. The possibility that treatment with phenobarbital predisposes to the shoulder-hand syndrome is discussed.

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#### Phénobarbital et syndrome épaule-main

##### RÉSUMÉ

Un traitement par le phénobarbital avec des doses et une durée variable fut trouvé dans les antécédents de 19 sur 29 cas de syndrome épaule-main bilatéral et chez 6 sur 46 malades présentant une atteinte unilatérale. Dans deux groupes de témoins d'âge et de sexe similaires comprenant respectivement des cas de périarthrite scapulo-humérale et de névralgie cervico-brachiale on trouva une consommation de phénobarbital significativement plus basse. On discute l'hypothèse d'une prédisposition possible au syndrome épaule-main à la suite de traitement par le phénobarbital.

#### Fenobarbital y el síndrome hombro-mano

##### SUMARIO

Una historia de tratamiento previo con fenobarbital de dosis y duración variable fué descubierta en 19 de 29 casos de síndrome hombro-mano bilateral y en 6 de 46 enfermos afectados unilateralmente. En dos grupos de testigos de edad y sexo similares comprendiendo respectivamente casos de peri-arthritis escapulo-humeral y neuralgia cervico-braquial el consumo de fenobarbital fué significativamente más bajo. Se discute la posibilidad de que el tratamiento con fenobarbital predispona al síndrome hombro-mano.