Thus our findings confirm that an elemental diet is an extremely useful method for inducing a remission in acute Crohn's disease, although it does not appear to protect against long-term relapse.

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Pituitary responsiveness to gonadotrophin-releasing and thyrotrophin-releasing hormones in children receiving phenobarbitone

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Summary and conclusions

The effect of long-term treatment with phenobarbitone on pituitary responsiveness to gonadotrophin-releasing hormone and thyrotrophin-releasing hormone was studied in 20 boys being treated with the drug to prevent febrile convulsions. Baseline concentrations of luteinising and follicle-stimulating hormones were reduced as well as the responses of these hormones to stimulation with gonadotrophin-releasing hormone. Baseline prolactin concentrations were raised in comparison with those in normal children. The response of prolactin to thyrotrophin-releasing hormone, however, was impaired only in the children who had been receiving the drug for a long time. Phenobarbitone had no effect on the secretion of growth hormone.

Further studies should be carried out to ascertain how long these effects on pituitary function last after phenobarbitone is withdrawn and whether this interference with pituitary function modifies the child's subsequent development.

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Introduction

Long-term treatment with anticonvulsants such as phenytoin and phenobarbitone is useful in preventing febrile convulsions in children. It is generally accepted that to be effective treatment with phenobarbitone should be continued for several months at doses ranging from 3 to 5 mg/kg body weight daily, even in children who have had only one febrile seizure.[1 2] Several centrally acting drugs interfere with the function of the

hypothalamus-pituitary axis. We do not know, however, of any available data on the effects of long-term treatment with anticonvulsants on pituitary function. We studied the effects of long-term treatment with phenobarbitone on the pituitary responsiveness to combined administration of gonadotrophin-releasing hormone and thyrotrophin-releasing hormone in children who were receiving the drug to prevent febrile convulsions.

Subjects and methods

We studied 20 boys being treated with phenobarbitone and 10 normal boys of comparable age. Ages ranged from 15 to 24 months. Ten children had been receiving the drug (Luminalette, 5 mg/kg body weight daily at 2000) for three to nine months (group A), while 10 had been under treatment for 10 to 20 months (group B). The purpose, details, and possible risks of the study were explained in detail to the parents, who gave their consent. Studies started at 0800, with the children fasting and recumbent. A 21-gauge scalp-vein needle was inserted in a cubital vein and patency achieved by a slow drip of physiological saline. After two baseline samples had been taken (at −15 and 0 minutes) all the subjects received an intravenous bolus of 25 μg synthetic gonadotrophin-releasing hormone (Relisorm) plus 100 μg synthetic thyrotrophin-releasing hormone (Relefact). Blood was collected 30, 60, and 120 minutes thereafter. Blood samples for hormone analysis were promptly centrifuged and serum aliquots stored at −20°C until required.

Serum concentrations of luteinising hormone were assayed by a specific double-antibody method[3] sensitive to 0·5 IU/l. Intra-assay and interassay variations were 2·5% and 11% respectively. Serum concentrations of follicle-stimulating hormone were assayed by a specific double-antibody method[4] sensitive to 0·5 IU/l. Concentrations of both these hormones are expressed as IU/l of the second International Reference Preparation human menopausal gonadotrophin. Serum prolactin concentrations were measured by a double-antibody method[5] sensitive to 1 μg/l. Intra-assay and interassay variations were 3·5% and 8·5% respectively. The results are expressed as μg/l. One microgram of the standard preparation used corresponds to 23 mU of the WHO 71/222. All the reagents used in assays of luteinising hormone, follicle-stimulating hormone, and prolactin were obtained from Biodata, Milan, Italy. Serum growth hormone concentrations were assayed by a specific radioimmunoassay using reagents obtained as a commercial kit from Sorin, Saluggia, Italy. The method is sensitive to 0·1 μg/l. Intra-assay variation was 5% and interassay variation 14%. Two-tailed paired and unpaired Student's *t* tests were used to analyse the data statistically. All the results are reported as means ± SEM.

Results

The tables show the results in the three groups of children. Under control conditions the serum concentration of luteinising hormone in the normal children was 5·1±1·04 IU/l (table I). This was significantly higher than the concentrations in groups A and B (2·25±0·52 and 1·15±0·07 IU/l respectively; $p<0·01$ in both cases). The average concentration of follicle-stimulating hormone in the normal children was 4·6±0·34 IU/l. This was not significantly different from the concentration of 3·21±0·28 IU/l found in group A ($p>0·05$) but was significantly higher than the 1·76±0·15 IU/l observed in group B ($p<0·01$). Administration of gonadotrophin-releasing hormone induced a prompt, significant increase in concentrations of both luteinising hormone and follicle-stimulating hormone in the normal subjects. Peak concentrations of both hormones occurred 30 minutes after injection (16·16±2·96 IU/l and 12·66±2·11 IU/l respectively; $p<0·001$). In patients in group A gonadotrophin-releasing hormone induced a significant increase in concentrations of luteinising and follicle-stimulating hormones to peak values of 9·85±1·93 and 7·66±1·98 IU/l respectively. The differences with respect to peak values observed in the normal subjects were significant ($p<0·01$ for luteinising hormone and $p<0·02$ for follicle-stimulating hormone). In patients in group B the injection of gonadotrophin-releasing hormone induced only modest increments in concentrations of luteinising and follicle-stimulating hormones, which, though significant with respect to baseline values ($p<0·01$), were significantly lower than those observed in the normal subjects ($p<0·01$) and patients in group A ($p<0·01$).

TABLE I—*Serum concentrations of luteinising hormone and follicle-stimulating hormone (IU/l) under control conditions and in response to administration of synthetic gonadotrophin-releasing hormone in normal children and children who had been receiving phenobarbitone for three to nine months (group A) and 10-20 months (group B)*

		Minutes after injection				
		−15	0	+30	+60	+120
Normal children (n=10)						
Luteinising hormone	Mean	5·18	5·10	16·16	12·83	6·30
	SEM	1·98	1·94	2·96	2·06	2·80
Follicle-stimulating hormone	Mean	4·83	4·16	12·66	9·33	5·20
	SEM	0·26	0·34	1·23	0·65	1·03
Group A (n=10)						
Luteinising hormone	Mean	2·30	2·25	9·85	8·00	3·36
	SEM	0·60	0·52	1·93	1·28	1·60
Follicle-stimulating hormone	Mean	3·26	3·21	7·86	5·25	3·60
	SEM	0·30	0·28	1·34	0·95	1·20
Group B (n=10)						
Luteinising hormone	Mean	1·14	1·15	4·36	2·70	2·01
	SEM	0·08	0·07	0·28	0·39	0·80
Follicle-stimulating hormone	Mean	1·78	1·76	5·60	4·30	2·16
	SEM	0·18	0·15	0·20	0·18	0·60

Under control conditions the average baseline prolactin concentrations were 11·06±1·95, 14·44±1·98, and 22·0±2·39 μg/l in the normal subjects, patients in group A, and patients in group B respectively (table II). Prolactin concentrations were higher in group B than the other groups ($p<0·01$). Administration of 100 μg synthetic thyrotrophin-releasing hormone increased prolactin concentrations in all the subjects studied. Peak concentrations were 42·0±4·50 μg/l in the normal children, 40·08±5·93 μg/l in the children in group A, and 29·67±1·26 μg/l in the children in group B.

TABLE II—*Serum prolactin concentrations (μg/l) under control conditions and in response to administration of synthetic thyrotrophin-releasing hormone in normal children and patients who had been receiving phenobarbitone for three to nine months (group A) and 10-20 months (group B)*

	Minutes after injection				
	−15	0	+30	+60	+120
Normal children (n=10)					
Mean	12·81	11·63	42·00	30·33	16·15
SEM	2·05	1·95	4·50	3·77	3·55
Group A (n=10)					
Mean	15·25	14·44	40·00	28·02	18·04
SEM	2·21	1·96	5·35	3·23	2·13
Group B (n=10)					
Mean	23·25	22·00	29·67	24·60	23·00
SEM	2·50	2·39	1·26	2·09	1·37

All these values were significantly higher than the baseline concentrations ($p<0·01$). Whereas no difference was found between the peak values observed in the normal children and those in group A, the difference between the peak concentrations in the normal children and the children in group B was highly significant ($p<0·001$).

Gonadotrophin-releasing hormone plus thyrotrophin-releasing hormone had no effect on serum concentrations of growth hormone. The average baseline concentrations of growth hormone were 1·34±1·25, 1·83±1·18, and 1·66±1·08 μg/l in the normal children and those in groups A and B respectively. No significant modifications were recorded throughout the observation period ($p>0·05$), nor were any side effects observed.

Discussion

The results of this study indicate that long-term treatment with phenobarbitone in children with febrile convulsions may modify basal as well as stimulated secretion of gonadotrophin and prolactin. Experimental data have shown that barbiturates may interfere with the release of gonadotrophins, presumably by acting on the central nervous system by inhibiting secretion of gonadotrophin-releasing hormone.[6 7] In particular, pheno-

barbitone may block spontaneous and gonadotrophin-stimulated ovulation in the rat, an effect that may be reversed by progesterone.[8 9] Our results show that pituitary responsiveness to gonadotrophin-releasing hormone is impaired during long-term treatment with phenobarbitone. This may be due to an effect on central nervous system sites, although direct action at the pituitary cannot be excluded. In contrast with previously reported experimental data, secretions of both luteinising hormone and follicle-stimulating hormone seem to be impaired.[6] Baseline prolactin concentrations were higher in the children treated with the drug than in the control subjects, the highest concentrations being observed in those treated the longest. While enhancing basal prolactin secretion, however, phenobarbitone reduced the release of prolactin induced by thyrotrophin-releasing hormone. Chronically raised prolactin concentrations may interfere with the pituitary-gonadal axis in man,[10] though this requires further elucidation. The raised prolactin concentrations observed in the children treated the longest might have contributed to the impaired pituitary gonadotrophin secretion. Long-term treatment with phenobarbitone has no effect on basal secretion of growth hormone. Moreover, no abnormal release of growth hormone was observed in response to gonadotrophin-releasing and thyrotrophin-releasing hormones. Although specific tests on secretion of growth hormone were not performed, this may indicate that the drug does not interfere with the neural and aminergic mechanisms controlling release of growth hormone in man.

If the results of the present study are confirmed on a larger number of patients, children treated with phenobarbitone should be studied to ascertain how long those effects on pituitary function last after withdrawal of the drug. Moreover, longitudinal studies may help to ascertain whether this interference with pituitary function leads to modifications in the child's development.

The skilled help of Mrs Jennifer Martin is gratefully acknowledged.

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ONE HUNDRED YEARS AGO We are happily absolved, by the absorption of our space with the proceedings of the annual meeting of the Association at Cambridge, from devoting much space to the unhappy proceedings in connection with the trial of the nurse Ingle for manslaughter of a patient at Guy's Hospital, in the wards of Dr Pavy, by the prolonged administration of a "punishment-bath," which produced an immediately injurious effect upon the patient, and accelerated her death. A few observations must, however, be made upon the facts before the public. In the first place, it is inconceivable in these days that there should have existed in the mind of any hospital nurse the theory that, under any circumstances whatever, she could be authorised to administer what is, to our amazement, spoken of calmly, and as a matter of justificatory description, as a punishment-bath. There are bad old traditions of the administration of torture of this kind in the bad old days of lunatic asylums, and in prisons; but they lingered in the recollection only as extinct abuses, classed with the gone-by horrors of the cruel jailer and the harsh keeper of an age which has passed away. A punishment-bath has long been recognised as a means not less dangerous than cruel, even when administered to strong and healthy persons. If we had heard of a punishment-bath ten years ago in a workhouse infirmary of the extinct class, as they existed before Dr Anstie and Mr Ernest Hart let in the light of day upon them, and swept away the abuses which still lingered in them as the worst and most corrupt existing refuge for the sick, we should have pointed to such an abomination as of itself enough to condemn the administration and its officers. To hear of the secret administration of torture or "punishment" by the bath by a nurse in one of our great public hospitals, the pride and glory of the metropolis, one of the chief seats of medical education, and where some of the greatest living medical men preside—or, as it now seems, are supposed to preside—over the wards, is not less surprising than it is shocking. We have said nothing on this subject while the trial was pending, lest it might seem to in some way prejudge the facts and prejudice the case of the prisoner; but, now that the case is over, we must say that the proof that such an act as the administration of a "punishment-bath," whether of an hour or an hour and a half, or indeed of ten minutes, could be possible in a metropolitan hospital, is a revelation. It is a revelation of the most grievous and startling kind, that the "lady-superintendent" of any hospital should so arrange the system of nursing, or should permit the existence of such a theory or spirit of nursing, as to make it possible that any nurse should think herself entitled to inflict physical punishment on sick people. That a nurse should drag an unwilling patient to a bath, is in itself an assault of an aggravated kind. That she should, as an act of punishment, immerse her in water for a prolonged period, is an assault of a peculiarly dangerous kind; and, whatever had been the issue, whether fatal or not, it cannot be said that a short term of imprisonment is too severe a punishment for so gross an offence. It reflects most severely upon the whole spirit existing in the nursing establishment of Guy's, that such an act should be possible. Even in prisons, when physical punishments are inflicted, the medical officer is informed beforehand, and his authority is recognised. But, happily, hospitals are not prisons or houses of correction; and it certainly is not the intention either of the public or of the medical profession that they should be converted into places of punishment for the sick. The theory that the nurse is to be told whether, in the opinion of the doctors, there exists in each patient a substratum of hysteria or the seeds of brain-disease, in order that she may of her own wisdom and mercy adjust the severity of the punishment which she may think it well to inflict to the capacity of endurance of the patient's diseased constitution, is altogether a new one. As the ingenious defence of an advocate, driven to invent a theory for the escape of the prisoner whom he is shielding, it is not devoid of striking originality and audacious effect. As a working guide for hospital management, it was reserved for the present lay administrators of Guy's Hospital to see such a state of things brought to light as to make it necessary for an able advocate to manufacture this theory on the floor of a criminal court, to mitigate the punishment awaiting the acts which have been proved to have occurred. We may well hope that such a state of things will soon cease. The sacrifice of principles to persons has surely been carried far enough; and this last ineffable disgrace to one of the greatest and most noble of our hospitals, whose history has been bound with traditions so very different, must surely point to the necessity of reversing a policy which has recently been one of personal bravado of the counsels and wishes of the medical officers, whose opinions and wishes ought certainly to be supreme in all that relates to the nursing of the patients, for whose well-doing they are mainly responsible. Two resignations would restore peace and efficiency; when will they be tendered? (*British Medical Journal*, 1880.)