ised simultaneously by the age of the mother at occurrence and by her age at interview.^{12 13} For a given age of occurrence the reported spontaneous abortion rate varies inversely and substantially with the interval since the occurrence. Such an effect is absent from data on reported stillbirth rates.¹⁴ This suggests that (presumably because of memory deficit) women are less likely to report spontaneous abortions occurring early in their histories than those occurring more recently. So the finding of Clarke *et al* and of Laurence and Roberts occurred in spite of this phenomenon and not because of it.

Incompleteness of sibships—It is not clear that this feature of the data has seriously biased the birth ranks of the miscarriages.

Compensation—There is good evidence that parents compensate after a miscarriage by starting another pregnancy.^{15 16} In such circumstances a Haldane-Smith test would yield a slight spurious suggestion of a negative birth order effect in the absence of a true one.¹⁷ It seems unlikely, however, that such a tendency could have affected the present results appreciably, if only because the sibships were incomplete.

The strongest bias (memory) was therefore working in the opposite direction to the present result. This suggests that the effect detected here is genuine and not a statistical artefact.

Discussion

The results seem to confirm speculation¹⁸ that miscarriages in ASB sibships show a negative birth order effect—that is, they are more likely to occur among the early than among the late birth ranks. This is in contrast to the position in random sibships, where there does not seem to be an overall negative birth order effect in spontaneous abortions.^{8 18} But ASB itself also shows a negative birth order (or at least primiparity)^{19–21} effect, which seems even more pronounced when some attempt is made to control variation due to social class.²² Taken together these facts seem to suggest that the additional spontaneous abortions in ASB sibships are not “normal” spontaneous abortions but further cases of ASB. Otherwise the question arises: Why do cases of ASB have a negative birth order effect

when their putative cause—miscarriages of fetuses without ASB—do not?

I am supported by the National Fund for Research into Crippling Diseases.

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(Accepted 20 October 1977)

Adrenocortical suppression in workers manufacturing synthetic glucocorticoids

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British Medical Journal, 1978, **1**, 73–74

Summary and conclusions

A man who had worked for 16 years in the manufacture of a potent corticosteroid was found to be suffering from chronic adrenocortical insufficiency attributed to chronic absorption of the glucocorticoid. Eleven other symptom-free workers were therefore screened. Two of these workers, like the first patient, gave grossly abnormal responses to the Synacthen (tetracosactrin) test; one had been employed for only seven months.

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All 12 men had facial plethora, suggesting absorption of the drug in spite of their having adhered to the safety precautions. All workers manufacturing potent steroids should therefore be screened regularly by measurement of their plasma cortisol concentrations and should be moved regularly to processing other drugs.

Introduction

Many studies have demonstrated adrenocortical suppression in patients receiving long-term steroid treatment for a variety of diseases^{1–5}; but such suppression has not previously been demonstrated in workers manufacturing synthetic glucocorticoid drugs. Our study was prompted by investigations on a man who had worked for 16 years at various stages of production of a potent corticosteroid.

Case report

Case 1—Although symptom-free while working, this man complained for two years of general ill health during periods of absence

from work, and of nausea and vomiting during the second week of holidays. He was suspected by his family doctor of having Cushing's syndrome because of his facial plethora; but plasma cortisol concentrations at both 10 pm and 9 am were less than 50 nmol/l (1.8 µg/100 ml). When he was referred to hospital, however, a Synacthen test gave a grossly abnormal result. The diagnosis was presumed to be chronic adrenocortical insufficiency due to chronic accidental absorption of the glucocorticoid.

FURTHER INVESTIGATIONS

The diagnosis of adrenocortical insufficiency in this patient suggested that other workers might be affected by absorption of the drug. Eleven men were therefore screened; they were aged between 27 and 53 years, and had been employed in the manufacture of synthetic glucocorticoid for between 7 months and 16 years. Careful histories were obtained, the emphasis being on any symptoms appearing during holidays and enforced absence from work. A clinical examination of each man was carried out. In each case routine urine analysis was performed and blood samples were obtained for estimating urea, electrolyte, and corticotrophin concentrations.

All the workers had an extended Synacthen test. Blood samples were obtained before the injection of 0.25 mg tetracosactrin and again 30, 60, and 90 seconds after it. All tests were assessed according to standard criteria of normality¹²: (1) a baseline cortisol concentration not lower than 170 nmol/l; (2) an increment rise of not less than 190 nmol/l; (3) a plasma cortisol concentration not less than 500 nmol/l after Synacthen. Plasma cortisol and corticotrophin concentrations were measured by using specific radioimmunoassay techniques. Insulin hypoglycaemia tests were not carried out in any patients.

Results

Two workers besides the first patient had grossly abnormal responses to Synacthen (see table), fulfilling none of the criteria of normality, although their plasma ACTH levels were normal.

Extended Synacthen tests in 12 workers involved in the manufacture of a synthetic glucocorticoid

Case No	Age	Duration of exposure (y)	Synacthen test—plasma cortisol (nmol/l)				
			0	30 min	60 min	90 min	30 min increment
1	42	16	39	116	102	135	77
2	42	3½	36	75	130	144	39
3	27	7½	17	127	237	304	116
4	53	1	135	472	701	682	337
5	31	2	461	569	712	555	108
6	29	6	585	751	1035	969	166
7	50	8	535	660	861	947	124
8	48	6	475	640	842	820	166
9	49	8	304	955	1151	1021	651
10	25	3	450	751	817	734	301
11	31	4	276	762	966	1145	486
12	45	16	243	731	897	977	489

Conversion: SI to traditional units—Cortisol: 1 nmol/l ≈ 0.04 µg/100 ml.

Case 2—This patient had been exposed for 3½ years. He was symptom-free and showed only facial plethora.

Case 3—This patient had been exposed for only 7 months. He was free of symptoms but was mildly Cushingoid, again with facial plethora, and had purple abdominal striae.

After admission to hospital all three affected patients received injections of Synacthen Depot on four consecutive days, and in each the plasma cortisol concentration rose to more than 800 nmol/l. They then received prednisolone, 5 mg on alternate days, the dose being gradually reduced over four weeks. Their morning plasma cortisol concentrations were consistently within the normal range.

Case 4—This patient, who had been exposed for a year, had a low basal cortisol concentration but a normal increment at 30 minutes, consistent with some adrenocortical reserve. His Synacthen test was performed after a four-week stay in a psychiatric hospital because of endogenous depression. Consequently he had not recently been

exposed to the drug and his result may represent gradual recovery of adrenocortical function after previous suppression.

In four other workers the incremental rise was low but the basal cortisol level was high, possibly reflecting the stress of their hospital visit. The remaining four workers had normal Synacthen tests. Urine analysis showed no abnormalities and plasma ACTH and electrolyte estimations gave normal results in all 12 workers. The only consistent clinical feature was facial plethora, which was found in each man.

Discussion

This study represents the first demonstration of adrenocortical suppression in workers manufacturing a potent synthetic glucocorticoid.

A dose of hydrocortisone sufficient to raise the plasma cortisol to 1400 nmol/l results in immediate cessation of ACTH secretion from the anterior pituitary.⁷ * As would be expected, a similar result can be obtained with a much smaller dose of betamethasone or dexamethasone.⁹ The adrenocortical suppression shown in four of our cases presumably results from appreciable chronic accidental absorption of glucocorticoid. Adrenocortical suppression is associated with dosage rather than duration of administration¹⁻³; it is alarming that one patient had been exposed for only 7½ months. The affected men worked in different parts of the manufacturing process and adhered strictly to the routine safety regulations.

In view of the plethoric appearance of all the men it seems likely that there had been prolonged facial contact with the drug. Nevertheless, ingestion or inhalation of the finely powered drug may be more important since the typical facial appearance was common to all the men irrespective of adrenocortical function.

It has been said that full assessment of hypothalamic/pituitary axis function is necessary in patients receiving synthetic glucocorticoids since some patients with a normal Synacthen response may fail to respond to the stress of insulin hypoglycaemia. In this study the normal men showed a response to Synacthen that was unequivocally normal, and it was thought inappropriate to carry out insulin stress tests in these symptom-free individuals.

In view of these findings we believe that workers manufacturing potent synthetic steroids are at risk despite adhering to recommended precautions. We suggest that all workers engaged in this process should have adrenocortical function tests and be screened at regular intervals by measurement of their morning plasma cortisol concentrations. Finally we recommend that such workers should have regular spells doing jobs concerned with non-steroid or non-physiologically-active corticosteroid drug processes.

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(Accepted 20 September 1977)