DISORDERS OF ENDOCRINE FUNCTION AFTER MAJOR HEAD INJURY

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S U M M A R Y

Outline of Study

Project Objectives

Description of Work Performed

OUTLINE OF STUDY

This study was instigated after the diagnosis of post-traumatic hypopituitarism in a young female under our care, who had sustained a closed head injury in a motor cycle accident (Case 1, see below). A review of the world literature revealed only 47 reported cases of post-traumatic hypopituitarism, with the majority occurring in the last 20 years (Edwards and Clark, 1986). Surprisingly, we were able to collect a further 5 cases over a relatively short period of time, suggesting that it might be a more frequent complication than is currently recognised. It is of interest that the low prevalence of clinical hypopituitarism is in contrast to the frequent finding of damage to the hypothalamus and pituitary by pathologists after fatal head injury (Daniel, Prichard & Treip, 1959; Ceballos, 1966; Kornblum and Fisher, 1969; Treip, 1970; Crompton, 1971; Harper et al, 1986).

As little endocrine information was available a large prospective study was undertaken to investigate abnormalities in endocrine function after head injury.

PROJECT OBJECTIVES

To determine

1. The endocrine response to major head injury.
2. The incidence of early hypothalamic and pituitary dysfunction following major head injury.
3. Whether secondary hypoadrenalism occurs and possibly contributes to early morbidity and mortality.
4. Whether results of early pituitary function tests correlate with the extent of brain injury and have an immediate prognostic significance.
5. The incidence of late neuroendocrine sequelae after severe head injury, in particular post-traumatic hypopituitarism.
6. The histopathological findings in the hypothalamus and pituitary in fatal cases, which together with the results from the pre-mortem endocrine tests should allow a detailed correlation to be made between structure and function.

DESCRIPTION OF WORK PERFORMED

Sixty patients who had sustained a major head injury were entered into the study. On admission to the Neurosurgical Unit a full clinical examination of each patient was performed. The cause of the accident, the direction of the injuring force, the results of in-patient investigations (including specialised neurosurgical radiology) and all medication were recorded. The severity of the injury was determined from the Glasgow Coma Scale and the duration of post-traumatic amnesia.

Within 24 hours of admission a venous blood sample for basal hormone concentrations and a dynamic test of anterior pituitary function, which consisted of the intravenous administration of 4 hypothalamic releasing factors (CRH, GRH, TRH and GnRH) with appropriate hormone samples collected during the ensuing 2 hours, were performed. A second set of endocrine tests were performed 1 week later and a final set during convalescence after 3-6 months.

As hypogonadism was frequently detected by these investigations, a further study examining the pulsatile release of LH was performed in 5 male subjects within 1 week of injury, with blood samples taken at 5 minute intervals for 6 hours. A further study to investigate central abnormalities of the gonadal axis, which involved intravenous infusion of naloxone, was stopped because of the naloxone's stimulant effect on these sedated patients.

Twelve of the 60 subjects died as a result of their injuries and a histopathological study of their pituitary glands and hypothalami was performed. The pre-mortem endocrine tests in these subjects were compared to the histological findings, to determine indicators of a bad prognosis.

C H A P T E R 1

REVIEW OF THE LITERATURE

Post-traumatic Hypopituitarism, with 6 Case Reports

Endocrine Response to Injury

Endocrine Studies performed after Head Injury

Investigation of Hypothalamo-Pituitary Hypofunction

Assessing Brain Damage after Head Injury

POST-TRAUMATIC HYPOPITUITARISM

This is defined as dysfunction of the anterior pituitary gland after injury, usually to the head. The first case was reported by a German physician, Cyran, in 1918 and involved a railway worker who had sustained a skull fracture when his head was trapped between a reversing wagon and buffers. Surprisingly, he survived the initial injury and subsequently developed loss of secondary sexual characteristics and hypothyroidism, presumed to be of pituitary origin (Cyran, 1918).

Cases were reported sporadically until an apparent recent upsurge, which may be due to several factors, including the increasing incidence of road traffic accidents, prolonged survival with improved intensive care and an increased awareness of the condition. The 6 cases collected in conjunction with my supervisor, Dr OM Edwards, make a total of 53 in the world literature (Table 1).

Case reports of the six local cases

Case 1:

This 16 year old girl was a pillion passenger on a motor cycle which collided with a car. The patient was wearing a crash helmet and did not sustain a skull fracture but she had fractures of the femoral neck, tibia and the arch of the first cervical vertebra. She remained unconscious for 3 weeks but the tendon

TABLE 1 Reported Cases of Post-traumatic Hypopituitarism

Case No.	Author(s)	Sex	Age at Diagnosis	Age at Injury	Trauma	Duration of Coma	Skull Fracture	Diabetes Insipidus	Neurological Sequelae
1	Cyran, 1918	M	48	32	Work inj.	Unknown	Base	No	CN 5
2	Reverchon & Worms, 1921	M	34	34	RTA	9 hrs	Base (sella)	Yes	CN 5, 6 & 7
3	Pascheff, 1922	M	-	-	Explosion	Unknown	Base	Temp	CN 1, 2 & 3
4	Schereschewsky, 1927	M	28	26	Fall	2 hrs	No	Yes	No
5	Gross, 1940	F	27	25	Fall	3 days	No	No	CN 1
6	Escamilla & Lisser, 1942	M	20	19	RTA	5 weeks	Yes	Yes	CN 2 & 7
7	Lerman & Means, 1945	M	46	15	Bullet	Several days	Bullet → fossa	No	Seizures
8	Lerman & Means, 1945	M	48	22	Explosion	Unknown	Unknown	No	Seizures
9	Porter & Miller, 1948	M	34	34	RTA	Several days	No	Yes	CN 2
10	McCullagh & Schaffenberg, 1953	M	25	22	RTA	2 weeks	Fronto-temporal	No	CN 5, 6 & 7
11	Lafon et al, 1955	F	33	33	Unknown	12 days	Unknown	No	No
12	Witter & Tascher, 1957	M	37	37	Blunt trauma	Several days	Occipital + base	Temp	CN 1 & Hemianaesthesia
13	Witter & Tascher, 1957	M	43	43	Blunt trauma	Several days	Base	Temp	CN 1 & Hemiparesis
14	Witter & Tascher, 1957	F	48	48	Blunt trauma	Momentary	No	No	CN 1
15	Goldman & Jacobs, 1960	F	22	15	RTA	Momentary	No	Yes	No
16	Werner, 1960	M	29	13	Bullet	1 week	Bullet → fossa	No	CN 2
17	Altman & Pruzanski, 1961	M	68	63	RTA	No	Fronto-temporal	No	CN 2 & 7
18	Linquette et al, 1968	M	27	26	Bullet	Unknown	Bullet → fossa	No	CN 2 & 3
19	Klachko et al, 1968	M	39	4	RTA	11 days	Base	Yes	CN 2 & Hemiparesis
20	Durand et al, 1969	M	62	60	Bullet	No	Bullet → fossa	No	CN 2
21	Pittman et al, 1971	M	19	12	Blunt trauma	1 minute	Unknown	Yes	No
22	Kanayama et al, 1972	M	46	20	Work inj.	33 days	Unknown	No	No
23	Woolf & Schalch, 1973	F	21	20	RTA	Several hrs	Base	No	No
24	Bevilacqua & Fornaciari, 1975	M	17	15	RTA	Unknown	No	Yes	No
25	Paxson & Brown, 1976	F	14	13	RTA	5 days	Temporal	Temp	CN 3
26	Dzur & Winternitz, 1976	F	30	26	RTA	Several days	No	Temp	No
27	Girard & Marelli, 1977	M	9	3	RTA	Several days	Yes	No	No

Case No.	Author(s)	Sex	Age at Diagnosis	Age at Injury	Trauma	Duration of Coma	Skull Fracture	Diabetes Insipidus	Neurological Sequelae
28	Weiss et al, 1977	F	22	20	RTA	Unknown	Facial	No	CN 2 & 7
29	Kanade et al, 1978	M	27	27	RTA	Unknown	Multiple (sella)	Yes	CN 2 & 3
30	Landau et al, 1978	M	32	32	RTA	Several days	Base	Temp	CN 2 & 6
31	Prosperi et al, 1978	M	12	12	Unknown	Momentary	Frontal	Yes	CN 2 & 6
32	Soules & Sheldon, 1979	F	23	23	Parachute	30 mins	Sella	No	No
33	Salti et al, 1979	M	32	32	Bullet	2 days	Bullet + fossa	No	CN 1, 2 & 7
34	Miller et al, 1980	F	11	4/52	Child abuse	Unknown	Unknown	No	Hemiparesis
35	Miller et al, 1980	M	11	5/52	Child abuse	Unknown	Parietal	No	Quadriplegia
36	Miller et al, 1980	M	7	10/52	Child abuse	Unknown	Unknown	No	Hemiparesis
37	Jambert et al, 1980	M	23	18	RTA	3 hrs	No	No	No
38	Notman et al, 1980	M	24	24	Blunt trauma	No	Temporal + base	Yes	CN 5, 7, 8, 9, & 11
39	Valenta & DeFeo, 1980	F	16	15	RTA	Unknown	Yes	No	No
40	Valenta & DeFeo, 1980	M	21	20	RTA	Unknown	Yes	No	CN 2 & 7
41	Pere et al, 1980	M	43	43	Work inj.	Several hrs	Base (sella)	Temp	No
42	Pere et al, 1980	M	49	27	Fall	Several days	Unknown	No	CN 6 & 7
43	Bistritzer et al, 1981	M	18	16	Fall	Several days	Base	No	CN 2 & Hemiparesis
44	Jambert et al, 1981	M	45	45	RTA	Several hrs	No	No	CN 2
45	Kaufman, 1981	M	20	20	RTA	1 week	Frontal	Yes	No
46	Fernandez-Castener et al, 1982	M	20	18	RTA	Unknown	No	Temp	No
47	Gomez-Saez et al, 1982	M	27	27	RTA	13 days	Multiple (sella)	No	No
48	Edwards & Clark, 1985	F	16	16	RTA	3 weeks	No	Yes	CN 2
49	Edwards & Clark, 1985	M	35	35	RTA	4 weeks	Frontal	Yes	No
50	Edwards & Clark, 1985	M	19	19	RTA	4 weeks	Frontal	No	CN 2
51	Edwards & Clark, 1985	M	48	47	RTA	24 hrs	Base (sella)	No	CN 1, 4, 6 & quadriplegia
52	Edwards & Clark, 1985	M	21	18	RTA	No	Temporo-frontal	No	No
53	Edwards & Clark, 1985	F	58	14	Shrapnel	Unknown	Shrapnel + fossa	Temp	No

Abbreviations: RTA = road traffic accident
CN = cranial nerve

reflexes were symmetrical with flexor plantar responses.

On admission cranial CT scan showed no displacement of midline structures but 3 weeks later, following the development of papilloedema, the repeat scan showed symmetrical dilatation of the lateral ventricles indicating active hydrocephalus. Bilateral ventriculo-atrial shunts were inserted. She gradually regained consciousness and after 3 months was transferred to the rehabilitation ward.

Shortly after transfer she developed galactorrhoea and was noted to have had no menstrual periods since the accident. Menarche had been at 12 years of age and her menses had been regular until the accident. She was not on an oral contraceptive or taking drugs known to cause lactation, and a pregnancy test was negative. She was found to be hypotensive with a plasma sodium concentration of 120 mmol/L and a low plasma cortisol at 0900 hours. She was given hydrocortisone replacement therapy, the plasma sodium concentration rose to normal and she became normotensive. The basal thyroxine level was low while the initial thyrotropin (TSH) level was elevated and the response to thyrotrophin releasing hormone (TRH) delayed (Table 2). The prolactin level was elevated and there was failure of luteinising hormone (LH) and follicle stimulating hormone (FSH) response to gonadotrophin releasing hormone (LHRH, GnRH). Five months after admission she developed polyuria and nocturia and the urine osmolality, after

TABLE 2 Endocrine tests on 6 patients with post-traumatic hypopituitarism (Authors' series)

	Basal Cortisol nmol/l	I.S.T. (0.1 U/kg) Plasma Cortisol nmol/l					I.S.T. (0.1 U/kg) GH mU/l					Thyroxine nmols/l	TRH (200 µg) TSH mU/l			TRH (200 µg) Prolactin mU/l			LHRH (100 µg) FSH U/l			LHRH (100 µg) LH U/l			Diabetes Insipidus
		Time (mins)																							
	0900h	0	30	60	90	120	0	30	60	90	120		0	20	60	0	20	60	0	20	60	0	20	60	
Case 1	<50	-	-	-	-	-	-	-	-	-	-	43	6.8	12	15	3000	2500	2900	<0.5	0.6	0.5	1.4	1.5	1.7	Yes
Case 2	110	-	-	-	-	-	-	-	-	-	-	30	3.5	8.4	9.9	1500	2700	2200	<0.6	0.5	0.6	0.4	0.8	1.2	Yes
Case 3	-	270	650	760	480	330	2.4	2.0	2.2	2.3	2.5	53	<0.4	0.9	1.1	540	750	850	<1	<1	<1	<1	1.9	2.0	No
Case 4	-	82	55	276	82	110	-	-	-	-	-	49	-	-	-	-	-	-	(<5mg equiv/24 hrs) NR 5-10)						No
Case 5	-	69	303	442	414	414	1.3	0.8	1.0	1.1	1.1	22	3	3.9	4.8	1260	-	-	0.6	0.8	0.7	2.7	2.1	2.2	No
Case 6	-	85	137	160	205	230	1	2.2	4.2	2.8	3.3	low*	-	-	-	840	-	-	5.0	7.3	9.4	4.1	12.6	20.8	Temp

Normal values:
1. Insulin Stress Test (blood glucose <2.2 mmols/l): Peak GH >20 mU/l, peak cortisol >550 nmols/l with increment >165 nmols/l.
2. TRH Test: Basal TSH 0-4 mU/l, peak TSH 6-22 mU/l.
   Males - Basal prolactin <350 mU/l, peak prolactin 400-1600 mU/l.
   Females - Basal prolactin <400 mU/l, peak prolactin 800-2000 mU/l.
3. LHRH Test: Males - Peak FSH 1.5-10.5 U/l. Peak LH 7-27 U/l.
   Females - Peak FSH 3-10 U/l. Peak LH 2.5-13 U/l.
4. Thyroxine 55-147 nmols/l, 0900 hours cortisol 200-650 nmol/l.

Abbreviations: I.S.T. = Insulin Stress Test
Temp = Temporary
*Iodine Uptake Test 13% (Normal range 25-55%).

water deprivation for 12 hours overnight, was 422 mOsm/kg, whilst the serum osmolality was 301 mOsm/kg. A diagnosis of partial cranial diabetes insipidus was made and she was commenced on intranasal desmopressin (DDAVP) with relief of her symptoms.

Four years after her injury she remains amenorrhoeic, has absent pubic and axillary hair and galactorrhoea. The prolactin levels remain elevated and there is complete failure of FSH and LH response to GnRH. She remains on desmopressin, thyroxine 0.15 mg daily, hydrocortisone 10 mg twice daily and more recently the combined oral contraceptive.

Case 2:

This 35 year old man was the driver of a van which was involved in a head-on collision in which he suffered a major closed head injury, associated with a depressed fracture of the left frontal bone and a fracture dislocation of the left acetabulum.

On admission he was unconscious and a cranial CT scan showed a contusion of the left temporal lobe and a left frontal haematoma. His condition deteriorated and the left frontal fracture was explored, the left frontal haematoma aspirated and a cranioplasty performed. He remained unconscious for 1 month, with 8 months of post-traumatic amnesia.

Immediately after admission the patient developed diabetes insipidus with a urine output of about 5 L/24 hr which responded to intramuscular desmopressin. Two

months after admission the desmopressin was stopped but the urine output rose in excess of 5 L/24 hr with a urine osmolality of 159 mOsm/kg and a plasma osmolality of 300 mOsm/kg. Two weeks after admission the 0900 hours plasma cortisol concentration was low, the level of thyroxine subnormal and the TSH response to TRH delayed (Table 2). The plasma testosterone level was also low, the LH and FSH response to LHRH absent and the prolactin level elevated.

Currently he remains on intranasal desmopressin, hydrocortisone 10 mg twice daily, thyroxine 0.15 mg daily and testosterone 100 mg every 3 weeks.

Case 3:

This 19 year old man, the driver of a motor car, was involved in a head-on collision during which he sustained a fronto-vertical fracture and was admitted unconscious. He developed decerebrate signs the following day and bifrontal and right temporal burr holes were made with the insertion of a left fronto-ventricular catheter and a right frontal subdural catheter. Contusion only was noted at operation. He remained unconscious for 1 month and on recovery of consciousness became over-talkative, euphoric and was noted to be perseverating. He was found to be totally blind due to bilateral optic nerve damage.

Over subsequent months he became hyperphagic, rapidly gaining 17 kg in weight. He was referred for endocrine assessment and was found to be obese (35%

above ideal body weight) with no clinical evidence of hypothyroidism or hypoadrenalism and his secondary sexual characteristics were normal. His fluid balance was normal with no nocturia and a water deprivation test showed normal rise of urine osmolality. There was no postural fall in blood pressure and the patient's temperature measured 4 hourly over 1 week showed normal circadian variation. An insulin stress test revealed a normal cortisol response but absent growth hormone response (Table 2). The thyroxine level was low with an absent TSH response to TRH, while the basal prolactin level was elevated. The testosterone level was low with no LH or FSH response to LHRH.

He remains on thyroxine and an intramuscular injection of testosterone every 3 weeks. He continues to be hyperphagic.

Case 4:

This 48 year old man was admitted unconscious and hypotensive with a flaccid quadriplegia and extensor plantar responses following a road traffic accident, in which he was involved in a head-on collision with a motor car. Blood stained cerebrospinal fluid was exuding from the nose and ears. Radiological examination revealed a basilar fracture through the sella turcica and rib and pelvic fractures.

He remained unconscious for 24 hours and in post-traumatic amnesia for 3 weeks. He was anosmic with 4th and 6th cranial nerve palsies. One week after admission

he became hypotensive and as he failed to respond to fluid replacement he was given an intravenous injection of hydrocortisone with rapid improvement. He was continued on dexamethasone until his endocrine assessment a month later.

An intramuscular injection of 80 units of ACTH was given daily for 4 days and the plasma cortisol rose to 932 umol/L on the last day. An insulin stress test showed a subnormal cortisol response (Table 2). His serum thyroxine was subnormal and his 24 hour urinary gonadotrophin excretion was less than 5mg equivalents/24 hours (normal range 5-10mg equivalents/24 hours). A water deprivation test was performed with a normal rise in urine osmolality.

He remains on hydrocortisone 30 mg daily in divided doses, thyroxine 0.2 mg daily and testosterone 250 mg every 3 weeks.

Case 5:

This 21 year old man was admitted following a road traffic accident when he was thrown off his motor cycle. On admission he was conscious but disorientated and no history of previous loss of consciousness was obtained. There were no focal neurological signs but a skull radiograph revealed a linear fracture of the right squamous temporal and frontal bones with a fluid level in the sphenoid sinus. He was discharged 4 days after admission and was well when reviewed 6 weeks later. Three years later he was referred with the

recent onset of tiredness, increasing cold intolerance, dizziness on standing and weight loss of 7 kg.

Pubertal development had been normal and until the accident he had shaved daily. Following the accident he shaved on alternate days and lost his pubic and axillary hair. He denied any impotency or diminution in libido but had noticed a failure of ejaculation.

On examination he was a pale young man with absent pubic and axillary hair and a sparse beard. The left testis was of normal size, while the right was absent. The blood pressure on standing fell from 110/70 mm Hg to 90/50 mm Hg. He had a sinus bradycardia and the reflexes were depressed.

An insulin stress test performed with the simultaneous administration of TRH and LHRH resulted in a subnormal cortisol and absent growth hormone response (Table 2). The thyroxine level was low, and there was an absent TSH response to TRH. The basal prolactin level was high and there was an absent FSH and LH response to LHRH. A skull xray showed the pituitary fossa to be of normal size.

He made an excellent recovery on replacement therapy of hydrocortisone 20 mg daily, thyroxine 0.2 mg daily and testosterone given by intramuscular injection.

Case 6:

This woman, born in 1925, started to menstruate when 11 years of age and continued to menstruate regularly until 14 when she was struck by shrapnel in the face and chest.

Immediately following injury she developed polyuria, polydipsia, hypersomnia and amenorrhoea. A skull radiograph showed a metal fragment lodged above the left side of the pituitary fossa. After a month in hospital she improved and was discharged but was readmitted 8 months later for investigation of mental retardation and continued amenorrhoea. She was found to have a right upper quadrantic homonymous hemianopia, the basal metabolic rate was subnormal and the blood pressure 100/70 mm Hg.

No active treatment was undertaken. She remained amenorrhoeic and at 27 years of age developed hot flushes. When aged 49 years she complained of cold intolerance, mental and physical retardation and marked weight gain; a clinical diagnosis was made of myxoedema which was confirmed by finding a low Iodine uptake. She was started on thyroxine replacement with relief of her symptoms and a weight loss of 38 kg.

When 58 years old she felt tired, mentally and physically lethargic, cold intolerant with anorexia and weight loss. She was found to have a normochromic normocytic anaemia, leukopaenia and thrombocytopaenia. A bone marrow biopsy showed slight loss of cellularity, normal megakaryocytes and diminished granulopoiesis.

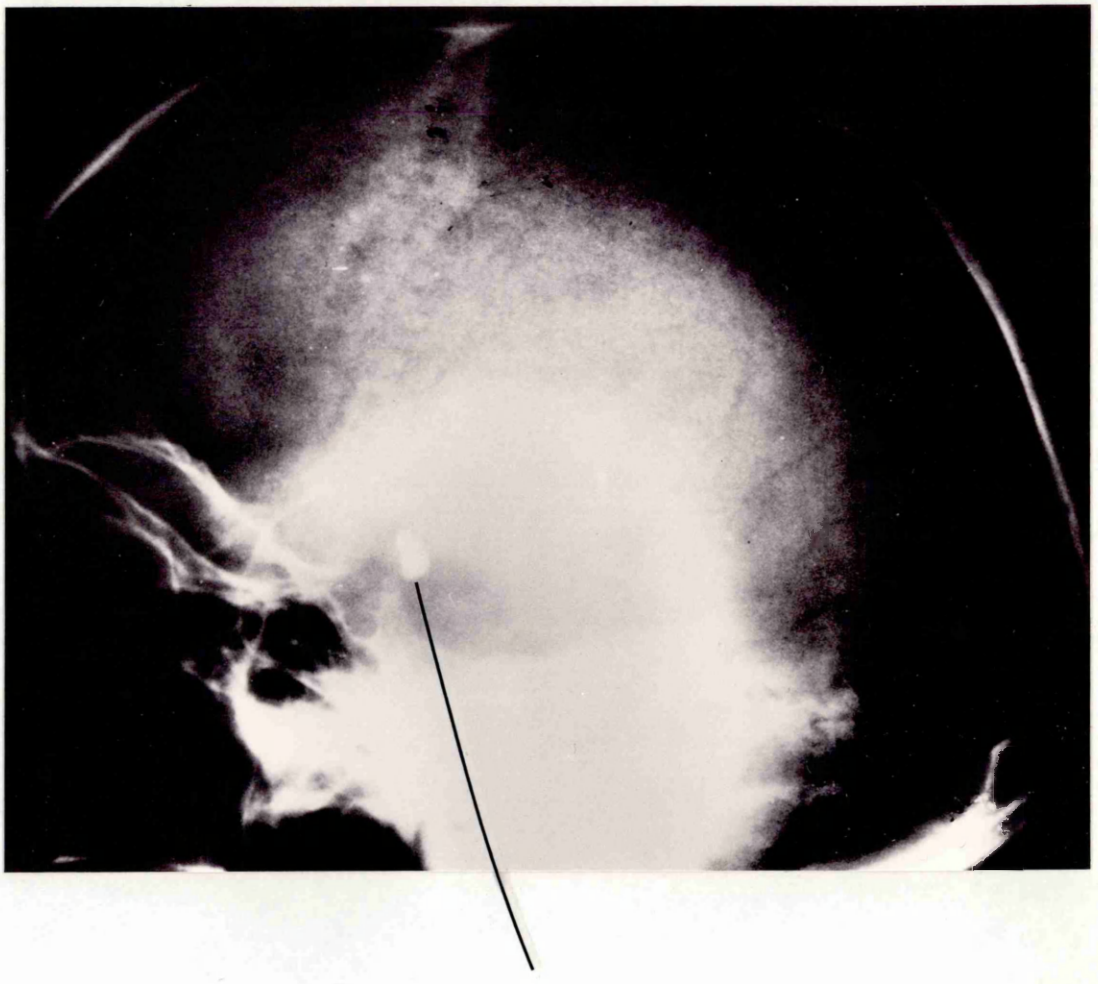
She had noted a gradual loss of pubic and axillary hair for many years.

On examination she had a pale facies with absent pubic and axillary hair, there was no postural hypotension or abnormal neurological signs.

An insulin stress test revealed a poor cortisol and growth hormone response, while the basal FSH and LH levels and their response to LHRH were less than expected in a post-menopausal woman (Table 2). The basal prolactin level was elevated. She was commenced on hydrocortisone 30 mg in divided doses in addition to her thyroxine 0.2 mg daily. The anaemia, leukopaenia and thrombocytopaenia resolved on this therapy.

Skull X-ray revealed a shrapnel fragment above and to the left of the pituitary fossa (Fig 1). A CT scan demonstrated that much of the pituitary gland and the left side of the hypothalamus had been destroyed, resulting in a small increase in size of the left lateral ventricle.

Figure 1 Skull X-ray demonstrating shrapnel fragment above pituitary fossa



Cause of Injury

Examination of the 47 cases in the literature together with our additional 6 cases revealed that post-traumatic hypopituitarism occurred mainly in young males, reflecting the high prevelance of death due to trauma in this age group. The most frequent cause of head injury was road traffic accidents, which were responsible for 27 of the 53 cases (Table 1). Occasional cases were reported after falls (Schereschewsky, 1927; Gross, 1940; Pere et al, 1980; Bistritzer et al, 1981;), work accidents (Cyran, 1918; Kanayama et al, 1972; Pere, 1980), direct bullet and shrapnel injury to the pituitary region (Lerman and Means, 1945; Werner, 1960; Linquette et al, 1968; Durand et al, 1969; Salti et al 1979 and our case 6), blunt trauma (Witter and Tascher, 1957; Pittman et al, 1971; Notman et al, 1980), bomb and blast injuries (Pascheff, 1922; Lerman and Means, 1945) and child abuse (Miller et al, 1980). The injury is usually to the head, the only exception being a patient who landed feet first on soft earth, after her parachute failed to open (Soules and Sheldon, 1979).

Skull fractures and direction of injuring force

Skull fractures were common, reflecting the seriousness of the impact (Table 1) and in the 47 cases reported, excluding the 6 with penetrating bullet or shrapnel wounds, 15 had fractures of the base of the skull, often involving the sella turcica, 9 had fractures of the frontal and temporal bones including 1 with associated basilar fractures and 2 had multiple skull fractures with associated basilar fractures. Only 3 patients had fractures of the facial skeleton or parietal and occipital bones. The fracture site was not specified in 4 cases and 11 cases did not have skull fractures (including our first case). In the remaining reports no information was given on the presence of a skull fracture.

Witter and Tascher (1957) considered that blows from behind and downwards commonly initiated pituitary damage and were often associated with fractures of the base or vertex of the skull, whereas Cebalos (1966), in a pathological study, demonstrated that in frontal injuries when the brain travelled backwards, the pituitary was constrained within the sella turcica, causing either disruption of the stalk or thrombus formation in the long portal vessels.

Neurological complications

Associated neurological abnormalities were common, the most frequent being blindness, either unilateral or bilateral with various field defects ranging from scotomata to homonymous hemianopia (Pascheff, 1922; Escamilla and Lisser, 1942; Porter and Miller, 1948; Werner, 1960; Altman and Pruzanski, 1961; Klachko et al, 1968; Linquette et al, 1968; Durand et al, 1969; Weiss et al, 1977; Kanade et al, 1978; Landua et al, 1978; Prosperi et al, 1978; Salti et al, 1979; Bistritzer et al, 1981; Jambert et al, 1981; Valenta and De Feo, 1982; and our cases 1 and 3). The next most common lesions were 5th, 6th and 7th cranial nerve palsies (Cyran, 1918; Reverchon and Worms, 1921; Escamilla and Lisser, 1942; McCullagh and Schaffenburg, 1953; Altman and Pruzanski, 1961; Weiss et al, 1977; Landua et al, 1978; Prosperi et al, 1978; Salti et al, 1979; Notman et al, 1980; Pere et al, 1980; Valenta and De Feo, 1980 and our case 4). Hemiparesis and hemianesthesia were less frequent (Witter and Tascher, 1957; Klachko et al, 1968; Miller et al, 1980; Bistritzer et al, 1981 and our case 4), with anosmia (Pascheff, 1922; Gross, 1940; Witter and Tascher, 1957; Salti et al 1979 and our case 4) and damage to other cranial nerves (Pascheff, 1922; Linquette et al, 1968; Paxson and Brown, 1976; Kanade et al, 1978; Notman et al, 1980 and our case 4) occurring in only a few cases. In many cases there were no neurological but only endocrine sequelae to head injury. In our six patients

there was a high incidence of associated neurological abnormalities ranging from complete blindness to spastic quadriplegia.

Patients were often unconscious for days or weeks but prolonged coma should not be regarded as a necessary accompaniment to traumatic hypopituitarism as several patients have either had no loss of consciousness or were unconscious for very short times (Witter and Tascher, 1957; Goldman and Jacobs, 1960; Altman and Pruzanski, 1961; Durand et al, 1969; Pittman et al, 1971; Prosperi et al, 1978; Notman et al, 1980 and our case 5).

Endocrine Findings in Post-Traumatic Hypopituitarism

There was adequate endocrine data on 26 patients (Tables 2 and 3). In most of these patients the basal levels of anterior pituitary hormones and their response to insulin-induced neuroglycopenia, TRH and GnRH were measured. Since most cases were diagnosed many months after the trauma, the time of onset of the hypopituitarism was not well-defined. The longest delay between injury and clinical presentation was 35 years (Klachko et al, 1968). However, studies of anterior pituitary function on patients developing diabetes insipidus shortly after head injury have revealed hypopituitarism to be present at 3 weeks (Barreca et al, 1980).

Gonadal function

Hypogonadism was a common presenting symptom of traumatic hypopituitarism and was clinically evident at the time of diagnosis, with amenorrhoea, impotence, loss of libido and loss of secondary sexual characteristics. The levels of the gonadal hormones and the basal gonadotrophins were low, and there was no response to a bolus injection of GnRH. One of our patients did have a response to GnRH, but less than would be expected in a post menopausal woman (Case 6).

However, the GnRH test cannot be used to distinguish between hypothalamic and pituitary causes of hypogonadotrophic hypogonadism (Mortimer et al,

TABLE 3 Endocrine tests on 20 patients with post-traumatic hypopituitarism

Author(s)	Insulin Stress Test		TRH			LHRH	Prolactin		Diabetes Insipidus
	GH Response	Cortisol Response	T4	Basal TSH	Stim. TSH	FSH/LH Resp.	Basal	Stimulated	
Pittman, 1971	Abs	N	L	L	N	-	-	-	Yes
Kanayama, 1972	Abs	Abs	L	N	Sub-N	-	-	-	No
Woolf, 1973	Abs	Abs	L	L	N	-	H	N	No
Ozur, 1976	Abs	Abs	L	N	N	-	H	-	Temp
Girard, 1977	Abs	Abs	L	L	Abs	-	-	-	No
Weiss, 1977	Abs	Abs	L	N	Abs	Abs	-	-	No
Kanade, 1978	Abs	Abs	L	N	Abs	Abs	N	Abs	Yes
Prosperi, 1978	Abs	Sub-N	L	N	Del-R	Abs	H	Abs	Yes
Salti, 1979	Abs	Abs	L	H	I	Abs	N	Abs	No
Soules, 1979	Abs	Abs	L	N	N	Sub-N	H	Abs	No
Barreca, 1980	Abs	Abs	N	N	N	Abs	H	N	Yes
Barreca, 1980	Abs	Abs	N	N	N	Abs	N	N	Yes
Valenta, 1980	Abs	Abs	L	H	N	Sub-N	H	Abs	No
Valenta, 1980	Abs	Abs	L	N	-	Sub-N	H	-	No
Miller, 1980	Abs	Sub-N	N	N	N	Sub-N	H	N	No
Jambert, 1980	Abs	Abs	L	N	Del-R	Abs	H	N	No
Jambert, 1981	Abs	Abs	L	N	N	Abs	N	N	No
Kaufman, 1981	Abs	Abs	L	N	Del-R	Abs	N	N	Yes
Fernandez-Castener, 1982	Abs	Abs	L	N	Del-R	Abs	H	-	Temp
Gomez-Saez, 1982	Abs	Abs	L	N	I	Abs	L	Abs	No

Abbreviations:

L = Low, N = Normal, H = High, Temp = Temporary.
Abs = Absent, Sub-N = Subnormal, Del-R = Delayed rise, I = Increased.
GH - Growth hormone. T4 - Thyroxine.
TSH - Thyroid stimulating hormone. TRH - Thyrotrophin releasing hormone.
FSH - Follicle stimulating hormone. LH - Luteinising hormone.
LHRH - Luteinising hormone releasing hormone (gonadotrophin releasing hormone).

1973), since in hypothalamic disorders repeated stimulation is often needed to ensure a normal LH and FSH response (Hashimoto et al, 1975).

Thyroidal function

Most of the patients were clinically and biochemically hypothyroid, with low thyroidal hormones, normal basal TSH levels and an absent TSH response to TRH. However, a few cases exhibited the phenomenon of hypothalamic hypothyroidism with low thyroidal hormones but a delayed, prolonged TSH response to TRH, as described by Faglia et al (1979). The TSH, in these cases, has recently been shown to have reduced biological activity due to impaired receptor binding (Beck-Peccoz, 1985).

Adrenal Function

Clinically, this is the most important axis because of the potentially fatal consequences of glucocorticoid deficiency. The cortisol response to stimulation was frequently subnormal, occasionally in subjects with no clinical evidence of hypoadrenalism (Barreca et al, 1980). Glucocorticoid replacement therapy was required in 23 of the 26 patients. The site of damage cannot be ascertained from the results of the insulin stress test as low basal levels of cortisol with a subnormal response to stimulation occur with damage to the hypothalamus and pituitary. However, the

hypothalamic releasing hormone, corticotrophin releasing factor (CRF), which acts directly on the pituitary corticotrophes (Grossman et al, 1982) may be of use in localising the damage since it has been shown to produce an exaggerated ACTH response in hypothalamic hypopituitarism and a subnormal ACTH response in pituitary-dependent hypopituitarism (Tsukada et al, 1984).

Growth Hormone

In all patients studied there was no growth hormone response to stimulation. In three children physical battering led to sub-dural haematomas in early infancy and decreased growth rates. Although short stature is well-recognised following child abuse, in particular the syndrome of psycho-social deprivation, the children described by Miller et al (1980) lacked the behavioural characteristics of psycho-social deprivation, and short stature occurred while in a caring environment. Endocrine tests revealed anterior hypopituitarism and the patients responded to growth hormone treatment. Two of the children had a delayed rise in TSH release following stimulation with TRH, which the authors interpreted as suggestive of a hypothalamic cause of the hypopituitarism. Thus all children with a serious head injury, regardless of cause, require long term observation for signs of impaired growth. The hypothalamic releasing hormone,

growth hormone releasing factor, may now be used to localise the site of damage in children.

Prolactin

This was elevated in the majority of cases and was associated with galactorrhoea in 4 of the 12 female patients (Woolf and Schalch, 1973; Dzur and Winternitz, 1976; Soules and Sheldon, 1979 and our case 1). It was thought to rise due to hypothalamic or stalk damage with release of lactotrophes from the prolactin-inhibiting factor, dopamine. Since the lactotrophes are located in the periphery of the gland, anterior pituitary necrosis could occur with destruction of other pituicytes leaving prolactin secretion unaltered (Soules and Sheldon, 1979). In a few patients the basal prolactin level was low, with an absent response to TRH, indicating extensive anterior pituitary necrosis.

Posterior pituitary function

Diabetes insipidus, either temporary of permanent, was a common finding and when present resulted in an earlier diagnosis of anterior pituitary failure. It occurred in 23 of the 53 cases, being temporary in 9. Its frequent association with anterior pituitary failure may stem from the fact that hypothalamic or upper stalk damage can produce both deficiencies. Temporary diabetes insipidus may either be due to inflammatory oedema in the hypothalamus or posterior

pituitary with resolution as the swelling settles or permanent damage to the posterior pituitary with persisting symptoms until antidiuretic hormone is directly released by neurons originating from the supra-optic and paraventricular nuclei (Lipsett et al, 1956).

Site of Endocrine Dysfunction

The pattern of endocrine abnormalities should vary according to whether the hypothalamus or pituitary is damaged. Injury predominantly involving the hypothalamus would produce low basal growth hormone and cortisol (ACTH) levels with no response to the stress of insulin hypoglycemia, low basal gonadotrophin levels with no response to a single bolus stimulation by GnRH, hypothyroxinemia with a variable TSH response to its releasing factor, hyperprolactinemia and temporary or permanent diabetes insipidus.

Predominantly pituitary damage would be expected to cause low basal levels of all six anterior pituitary hormones with no response to stimulation, since the hormone producing cells are destroyed, and occasionally diabetes insipidus depending on the level of stalk injury.

However, only a few cases had all the features of typically hypothalamic (Dzur and Winternitz, 1976; Prosperi et al, 1978 and our cases 1 and 2) or pituitary (Gomez-Saez et al, 1982) dysfunction. Presumably, in most cases injury is sufficient to

damage both structures producing a mixed endocrine picture.

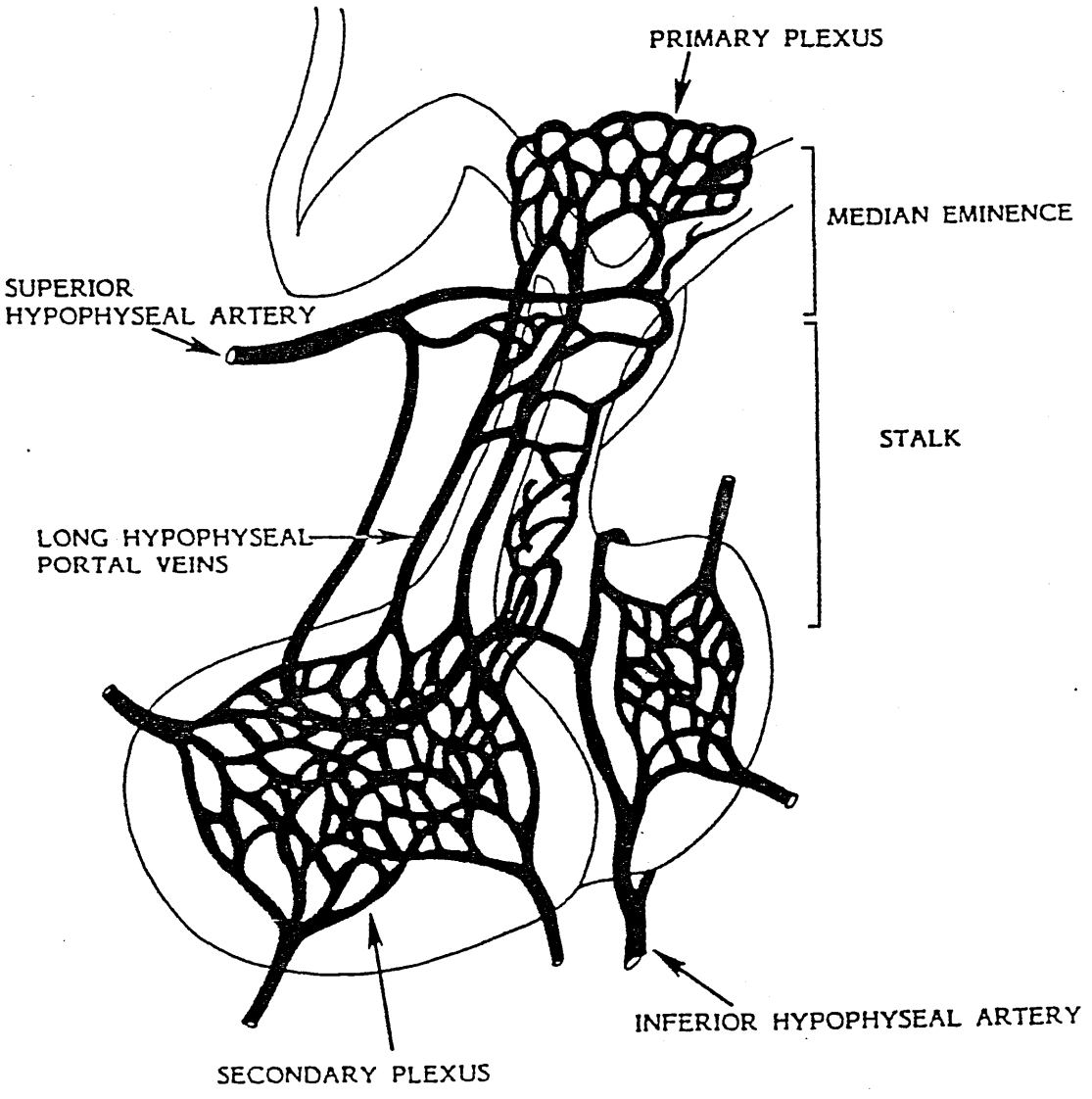
Pathological Findings in the Hypothalamus and Pituitary after fatal head injury

Pathological changes in the hypothalamus and pituitary are commonly found in patients dying of head injury. Massive infarction of the anterior pituitary following head injury was first described by Daniel et al (1959 b), who reported 6 cases. They suggested that this occurred due to interruption of the blood supply to the anterior pituitary and warned that pituitary infarction should be borne in mind in patients who remain in prolonged coma.

Pituitary findings

Daniel and his co-workers had previously demonstrated the unique blood supply to the anterior pituitary gland, which renders it susceptible to hypotension and trauma (FIG 2). Using injection techniques (Xuereb, Prichard and Daniel, 1954) showed that the anterior lobe has no arterial blood supply but that it is supplied with blood only through the hypophyseal portal blood vessels. Thus all the blood reaching the anterior lobe has already passed through a primary capillary bed lying in the median eminence and pituitary stalk. There are two types of portal vessel supplying blood to the anterior lobe, the long and

Figure 2 Blood supply of pituitary gland and stalk



short portal vessels. They are both derived from the primary capillary bed but the short portal vessels emerge from the lower part of the pituitary stalk below the level of the diaphragma sellae. The long portal vessels supply upto 90 % of the anterior lobe and the short portal vessels supply a variable layer of anterior lobe cells adjacent to the posterior lobe. The inferior hypophyseal arteries supply the posterior lobe.

There have been 4 studies of the pathological changes in the pituitary following fatal head injury (Daniel and Treip, 1961; Ceballos, 1966; Kornblum and Fisher, 1969; Harper et al, 1986), since the initial observations by Daniel et al in 1959. Differences exist between the classification system used in the various studies but most divided anterior pituitary necrosis into small and large infarctions (large defined as affecting 80% or more of the cross sectional area of the anterior lobe). In addition two studies examined the histological changes in the hypothalamus (Treip, 1970; Crompton, 1971).

Large anterior pituitary infarcts had a similar distribution in all studies, residual parenchyma being restricted to a narrow subcapsular band and a broader wedge adjacent to the posterior lobe. Small infarcts occurred in any part of the lobe and were occasionally multiple. Haemorrhage within the anterior lobe was uncommon and occurred more frequently in the posterior lobe. Infarcts in the posterior lobe were infreqent and

when present were associated with large anterior lobe infarcts. Table 4 summarises the findings with respect to the pituitary gland in these 5 studies.

Various mechanisms have been suggested to explain the typical central distribution of the large anterior pituitary infarct. Daniel et al (1959 a) observed that when the pituitary stalk is cut at the operation of stalk section and the pituitary gland is examined within a few days of operation most of the anterior lobe is infarcted. Adams et al (1963) measured the infarct size in one such case and found it to be 90 % of the volume of the anterior lobe. The only surviving tissue is a thin layer of cells (only a few cells thick) extending like a capsule round the gland and a layer of variable thickness adjacent to the posterior lobe. The large central infarct is due to interruption of the long portal vessels. As the stalk is cut above the diaphragma the blood supply to the posterior lobe (inferior hypophyseal arteries) is not interfered with but the posterior lobe is denervated. These arteries also supply the short portal vessels thereby explaining the presence of surviving tissue next to the posterior lobe. The small capsular arteries are thought to explain the thin layer of viable cells surrounding the gland. The striking similarity in surviving tissue and infarct distribution led Daniel et al (1959 b) to suggest that stalk section produced by head injury was the mechanism responsible for the observed massive pituitary necrosis.

Table 4 Pathological studies on the pituitary gland following fatal head injury

	No. of Cases	No Abnormality	Ant. Lobe Infarction		Post. Lobe Haemorrhage		Stalk Haemorrhage/Thrombus	Capsular Haemorrhage
			Small	Large	Small	Large		
Daniel & Treip, 1961	152	56	5	8	49	20	8	No data
Ceballos, 1966	102	14	11	11	4	16	28 (6 necrosis)	59
Kornblum & Fischer, 1969	100	38	22*		42*		6 (1 stalk section)	59
Crompton, 1971	53	No data	7*		7*		No data	No data
Harper et al., 1986	100	No data	25	13	12*		1	No data

* = Size unspecified

However later studies involving larger numbers of cases noted that stalk section was found much less frequently than anterior pituitary necrosis and concluded that it could not be responsible for the necrosis in the majority of cases. Kornblum and Fisher (1969) suggested that confinement of the pituitary gland in the sella turcica by the diaphragma sella makes the stalk especially vulnerable to shearing strain. Subsequent swelling of the gland is limited by the diaphragma sella, which has only a small circular opening serving as a passage for the pituitary stalk. As it swells the fragile long hypophyseal vessels are compressed between the stalk and the free edge of the diaphragma sella resulting in anterior pituitary infarction. The short hypophyseal vessels arising below the diaphragma are not affected. Harper et al (1986) agreed with Kornblum and Fisher, stating that the blood flow through the hypophyseal portal vessels may be interrupted without actual transection of the stalk. In his study all cases with a large or medium sized infarct had raised intracranial pressure and many also had significant mid-line shift. This combination of factors may be sufficient to impair the portal blood supply on the stalk.

Several authors have reported an association between basal skull fractures and anterior pituitary necrosis, particularly if the fracture affects the pituitary fossa (Daniel and Treip, 1961; Harper et al, 1986). In these cases the injuring force is transmitted

through the base of the skull to the region of the pituitary, resulting in pituitary damage. The direction of force most likely to result in pituitary injury is undecided; some studies (Crompton, 1971) suggest that lateral impact in the tempero-parietal region is more likely to produce pituitary damage, whereas others (Ceballos, 1966) suggest that maximum stretching and jarring of the pituitary occurs with fronto-occipital impact.

Hypothalamic lesions

Hypothalamic injury was relatively common and in Crompton's study (1971) of 106 cases of fatal head injury he found lesions in 45 cases; microhaemorrhages in 31 and ischaemic necrosis in 26. The microhaemorrhages were mainly found in the supraoptic and paraventricular nuclei, the median forebrain bundle and the median basal eminence, while ischaemic lesions had a haphazard distribution. Treip (1970) confirmed this predilection for the supraoptic and paraventricular nuclei and postulated that it was due to the tethering of the optic nerve to the optic foramen by a dural sheath while caudally it forms an angle with the lamina terminalis within which the supraoptic nucleus lies. Thus, as one side of the angle is fixed, sudden movement of the brain such as occurs with head injury could readily lead to shearing of the rich supply of thin walled vessels to this nucleus with consequent haemorrhage. Infarction was common in the

median eminence and the upper stalk, leading to pooling of neurosecretory material due to disruption of the supraoptico-hypophyseal tract (Treip, 1970). The vulnerability of this area could be explained by the traction exerted on it and its blood supply by the pituitary stalk which is tethered below to the diaphragma sella.

The majority of the studies draw attention to the disparity between the relatively high incidence of hypothalamo-pituitary damage in the pathological literature compared to the paucity of clinical reports of post-traumatic hypopituitarism. In the most recent study Harper et al (1986) concluded that hypothalamo-pituitary damage is common in patients with head injury and although many patients with large pituitary infarcts may die as a result of the effects of increased intracranial pressure and distortion of the brain, clinicians should be more aware of this treatable endocrine complication of head injury.

THE ENDOCRINE RESPONSE TO INJURY

Physiology

The neuroendocrine response to injury may begin before the injury itself, with awareness of approaching danger activating the hypothalamus. This results in the secretion of several pituitary hormones including ACTH, GH, PRL and vasopressin, activation of the sympathetic nervous system and, as a consequence of the ACTH release, increased cortisol secretion. Once the injury has occurred this stress response is reinforced by stimuli from nociceptive afferents in damaged tissue (Stoner, 1976). Conscious perception of pain is not necessary, as the neuroendocrine response occurs in surgical patients under anaesthesia. It is not clear how the impulses reach the hypothalamus, although the spinoreticular or spinomesencephalic tracts may be involved (Willis, 1984). Hypovolaemia also contributes to the response with decreased inhibitory neural input from the low pressure baroreceptors in the right atrium and, if the blood pressure falls, from high pressure ones in the carotid arteries. The stimuli reach the hypothalamus via the tractus solitarius and the medullary reticular formation (Gann and Lilly, 1984).

This early phase after injury is characterised by rapid mobilisation of glycogen and lipid stores, although the metabolic rate is not raised to the extent expected from the degree of fuel availability (Little, 1985). In 1942 Cuthbertson termed this phase of

mobilisation of fuel stores, together with apparent restraint on their utilisation, as the ebb phase. This lasts typically around 12-24 hours depending on the severity of the injury and the treatment given. It merges into a more prolonged period characterised by an increase in metabolic rate and a breakdown of body tissues, the catabolic or Cuthbertson's flow phase of the response to injury. The duration and intensity of this phase varies according to the severity of the injury (Wilmore, 1977) but in orthopaedic patients with long bone fractures it merges into the anabolic or convalescent phase over the next 2-4 weeks (Frayn, 1986).

The neuroendocrine control of metabolism is most obvious in the ebb phase when there is a large sympathetic discharge, reinforced by pituitary stimulation of cortisol secretion. This phase is characterised by fuel mobilisation and many of the hormones secreted have potential roles in promoting glycogenolysis and lipolysis. Adrenaline appears to have the major role in liver glycogen breakdown as the resultant hyperglycaemia is correlated to the plasma adrenaline concentration (Frayn et al, 1985). Similarly, the elevated plasma lactate concentration in injured patients, thought to arise from muscle glycogenolysis (Daniel et al, 1978), bears a weak but significant relationship to plasma adrenaline concentration (Frayn et al, 1985). In addition adrenaline, cortisol and glucagon act synergistically

to promote and sustain hepatic gluconeogenesis (Shamoon et al, 1981). Lipolysis is also stimulated by catecholamines and may be potentiated by cortisol (Fain, 1980) and the high GH levels reached soon after injury (Frayn et al, 1984 b). As cortisol levels are variable shortly after injury, often being lower in the more severely injured (Barton, 1987), and because the actions of cortisol are mediated through enzyme induction it seems probable that the role of cortisol is concerned more with maintenance than with initiation of this response. Thus, when the glucocorticoid response to injury is blocked in animals the hyperglycaemic response is transient rather than sustained (Frayn, 1986).

The flow phase of the response to injury is characterised by an increased metabolic rate, an elevated core temperature and pulse rate, and increased urinary excretion of nitrogen together with other markers suggestive of net muscle protein breakdown (Cuthbertson, 1930 and 1980). The hypermetabolism is initially due primarily to an increased rate of fat oxidation (Frayn et al, 1984 a). This response may have evolved to encourage wound healing as the wound's requirement for glucose necessitates protein breakdown to provide amino acids as a gluconeogenic substrate and the gluconeogenesis requires energy derived from fat metabolism (Frayn, 1986). As the counter-regulatory hormones, adrenaline, cortisol, glucagon and GH, together produce a generally catabolic state, with

stimulation of lipolysis, glycogenolysis and gluconeogenesis, much attention has focused on their potential role in producing this metabolic pattern. However the time course of their responses do not fit with the characteristic time sequence of the flow phase metabolic changes. The concentration of these hormones is high during the ebb phase but there is a fairly rapid return towards normality, such that at the time of the peak catabolic response 7-10 days after injury, there may still be a moderate elevation of plasma cortisol, depending on severity (Frayn et al, 1983), but the concentrations of GH, glucagon and catecholamines are likely to be back into the normal range (Frayn, 1986). Furthermore infusion of catecholamines, cortisol and glucagon in combination to simulate the response to injury have produced metabolic changes of only modest degree (< 10% elevation of metabolic rate, 4 g/day rise in urinary nitrogen excretion) (Gelfland et al, 1984; Bessey et al, 1984). Thus although the counter-regulatory hormones contribute to the flow phase metabolic picture other, as yet unknown, mechanisms must have a significant role.

THE ENDOCRINE RESPONSE TO INJURY

ADRENAL AXIS

Central control

Since 1948, when Harris demonstrated that the neural control of the pituitary-adrenal axis was mediated by chemical substances released from nerve terminals in the median eminence into hypophyseal portal vessels, researchers have been attempting to isolate a single hypothalamic corticotrophin releasing factor. However it is now apparent that ACTH secretion is controlled by several neuropeptides.

In 1981 Vale et al identified a 41 amino acid peptide, called CRF-41, which is now accepted as the major releasing factor for ACTH. CRF-41 is produced by neurons which originate in the paraventricular nucleus and terminate in the vessels of the primary plexus in the median eminence (Buckingham, 1985). Thus like the other releasing factors, it is secreted directly into the hypothalamo-hypophyseal portal vessels. Deficits in stress-induced ACTH release caused by hypothalamic cuts have been correlated with CRF-41 immunoreactivity in the median eminence (Tilders et al, 1982). However when CRF-41 antisera is administered the ACTH response to stress is not completely inhibited, indicating that there must be other corticotrophin releasing factors.

There is considerable evidence that vasopressin is an important factor in the control of ACTH secretion

(Gillies and Lowry, 1979) and immunocytochemical studies indicate that CRF-41 and vasopressin are contained within the same neurons in the paraventricular nucleus (Roth et al, 1982). However immunoneutralisation of both peptides (Berkenbosch et al, 1984) still fails to completely abolish the stress induced release of ACTH. Other factors which may modulate ACTH release include oxytocin, angiotensin 2 and adrenaline (Rivier and Vale, 1983; Gaillard and Al-Damluji, 1987). It has been suggested that the different ACTH secretagogues activate the hypothalamo-pituitary-adrenal axis in response to different forms of stress (Gaillard and Al-Damluji, 1987). They can also act together synergistically as the ACTH response to crude hypothalamic extracts is greater than the ACTH response to any of the secretagogues given individually (Gillies et al, 1982).

The activity of the CRF-41 secreting neurons is controlled primarily by excitatory and inhibitory neural pathways originating from other parts of the CNS. Studies in laboratory animals involving electrical stimulation or lesions of specific brain areas have illustrated the roles of the amygdala, hippocampus, thalamus, basal septal area and rostral midbrain reticular formation in the neural pathways (Knigge, 1961; Buckingham, 1985). Cholinergic, catecholaminergic and 5-hydroxytrytaminergic neurons (5-HT) appear to stimulate CRF-41 secretion in man (Buckingham, 1985). GABA-ergic neurons exert a tonic inhibitory influence

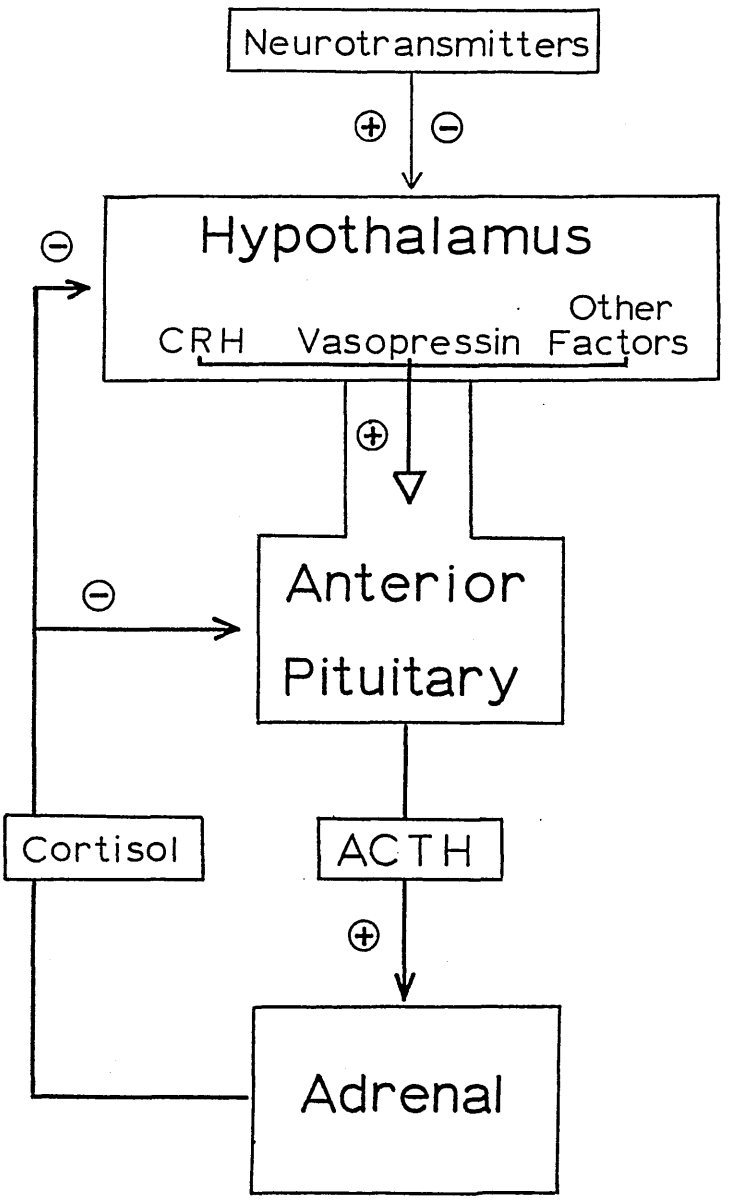
over the hypothalamic secretion of CRF and similarly opioid peptides inhibit the release of ACTH and related peptides (Buckingham, 1985) (Fig 3).

ACTH and cortisol responses to injury

Shortly after it was discovered in 1936 (Coller et al, 1936) that there was an impairment in sodium excretion after surgery, Weil and Browne (1939) showed that urinary corticoid excretion was simultaneously increased. These observations after surgery were confirmed (Venning et al, 1944; Bennett and Moore, 1951) and Bliss et al (1953) demonstrated that the increase in urinary steroid excretion was associated with increased plasma concentrations of 17 hydroxycorticoids. Subsequently similar changes were recorded in subjects following injury (Hume et al, 1956; Moore, 1957).

More recent studies have investigated plasma ACTH and cortisol responses to injury. Acute trauma stimulates the secretion of ACTH (Buckingham, 1985) and within a few hours of accidental injury some patients have elevated ACTH concentrations sufficient to produce maximal stimulation of the adrenal cortex (Barton, 1987; Barton et al, 1987). However there was great variety in the ACTH levels, which correlated poorly with plasma cortisol and some of the most seriously injured patients had ACTH levels within normal limits (Barton et al, 1987). Variable ACTH levels have also been reported after burns, with a lack of association

Figure 3 Central Control of the Adrenal Axis



between ACTH levels and increasing severity of burn (Dolecek et al, 1979; Vaughan et al, 1982; Brizio-Molteni et al, 1982). It is of interest that these 3 studies have reported relatively low values of ACTH in some patients with extensive thermal injuries. It has been suggested that in this group of patients there may be an increase in the sensitivity of the adrenal cortex to ACTH or that factors other than immunoreactive ACTH may be stimulating cortisol secretion (Barton, 1987). During surgery plasma ACTH levels have been found to increase to a maximum 0.5-4 hours after the start of operation, returning to preoperative levels after 24 hours (Cooper and Nelson, 1962; Newsome and Rose, 1971; Oyama et al, 1979). In contrast to accidental and thermal injury Newsome and Rose (1971) demonstrated that cortisol and ACTH levels were correlated and Ney et al (1963) showed that the relationship between them was similar to normal subjects given ACTH at different rates.

Plasma cortisol increases following trauma of any kind, including surgery (Johnston, 1964; Gill et al, 1975), long bone fracture (Frayn et al, 1983), multiple injury (Carey et al, 1971), myocardial infarction (Frayn, 1986), burns (Vaughan et al, 1982) and head injury (King et al, 1970; Steinbok and Thompson, 1979). The level rises within the first few hours after trauma (Johnston, 1964; Gill et al, 1975; Stoner et al, 1977; Stoner at al, 1979) and the diurnal pattern of cortisol secretion is lost, with elevated values occurring

throughout the 24 hour cycle (Thomasson, 1959; Wise et al, 1972 b; Molteni et al, 1979; Steinbok and Thompson, 1979; McIntosh et al, 1981). The duration of the elevated cortisol level depends on the severity of the injury. After moderate injury the level starts to fall within the first few days but does not reach normal levels for over a week (Barton and Passingham, 1981; Frayn et al, 1983; Frayn et al, 1984 a). The elevation may extend to weeks if the injury is sufficiently severe (Batsone et al, 1976) or the patients are elderly (Frayn et al, 1983). Following burns cortisol levels are often elevated for longer than 2 weeks (Wise et al, 1972 a; Batsone et al, 1976; Vaughan et al, 1982), whereas after surgery normal concentrations are usually regained by 4 days (Moore, 1957; Thomasson, 1959). Some workers have demonstrated that the extent of the rise also depends on the severity of the injury (King et al, 1970; Steinbok and Thompson, 1979; Vaughan et al, 1982). However other workers have shown that although there is a positive relationship between plasma cortisol levels within 8 hours of injury and moderate injuries, if the injury is severe the cortisol level is frequently lower and a negative relationship is present (Stoner et al, 1979; Barton et al, 1987). It has been suggested that in severely injured patients diminished adrenal blood flow may be responsible for the lower cortisol levels (Barton et al, 1984).

Alteration in feedback mechanisms

It has been suggested that the immediate effect of trauma is to increase the set point of the corticosteroid feedback centre (Yates et al, 1961). Thus the pituitary gland is provided with a signal similar to a decrease in the blood cortisol concentration and ACTH secretion continues until the new set point in the plasma cortisol concentration is reached. Three studies in head injured patients have suggested that the centre monitoring corticosteroid feedback is altered by injury. McCarthy et al (1964) observed that 4 of 11 patients had no increase in urinary steroid excretion after receiving metyrapone and 3 failed to suppress urinary steroid excretion with dexamethasone. Steinbok and Thompson (1979) studied one patient whose plasma cortisol levels were initially suppressed by 40 mg of dexamethasone daily but as the dose of dexamethasone was reduced the plasma cortisol level rose again, reaching abnormally high levels while dexamethasone was being administered in a dose which would normally maintain suppressed levels. This could indicate that the feedback control centre for glucocorticoids was set at a higher level than normal. Feibel et al (1983) confirmed that cortisol was resistent to suppression with dexamethasone after head injury, particularly if intracranial pressure was raised.

Other workers performing experiments involving the acute administration of corticosteroids to rats suggest

that the hypothalamo-pituitary-adrenal response to trauma is independent of the plasma corticosteroid concentration at the time of the stimulus. Inhibition of ACTH release occurred only some time after the blood corticosterone concentration had returned to the resting level, indicating that a delayed feedback mechanism modulates the pituitary-adrenal response to stress (Smelik, 1963). A rapid feedback mechanism has also been implicated in the control of trauma induced hypothalamo-pituitary-adrenal activity and Dallman and Yates (1969) demonstrated an immediate but short (less than 5 min) period of inhibition of the pituitary-adrenal response to trauma in rats during infusion of corticosterone.

Mechanism of adrenal axis activation

Many factors associated with injury can activate the adrenal axis; hypovolaemia via the carotid and aortic baroreceptors activates neural pathways to the CNS, and emotional stimuli (such as fear and anxiety) acts centrally, but probably the most important stimulus involves neural impulses from damaged tissues. Hume et al (1962) showed in dogs that the increased cortisol secretion rate was dependent on an intact nerve supply to the injured area and Eisentein et al (1962) showed that injury to the lower limbs of paraplegics did not result in elevated cortisol levels. However the response to surgery performed under spinal anaesthesia is reduced but not abolished (Lush et al,

1972; Gordon et al, 1973). Enquist et al (1977) have demonstrated that autonomic afferent fibres are the primary mediators of the cortisol response during pelvic surgery, whereas both autonomic and somatic nerves are involved in the hours following surgery (Christensen et al, 1982).

How the various stimuli regulate trauma-induced CRF secretion is unknown although it has been suggested that a reduction in opioidergic tone or stimulation by 5-HT neurons may be partially responsible for the rise in plasma cortisol concentration (Buckingham, 1985).

Summary

Both ACTH and cortisol levels increase in response to any form of injury, with loss of diurnal rhythm. The duration of the increased cortisol level is related to the severity of injury and can remain elevated for more than a week. A subgroup of patients with severe injuries have lower cortisol levels than expected, possibly related to diminished adrenal perfusion. There are many factors after injury which may activate the adrenal axis and some may be operating by resetting the glucocorticoid negative feedback centre.

GROWTH HORMONE

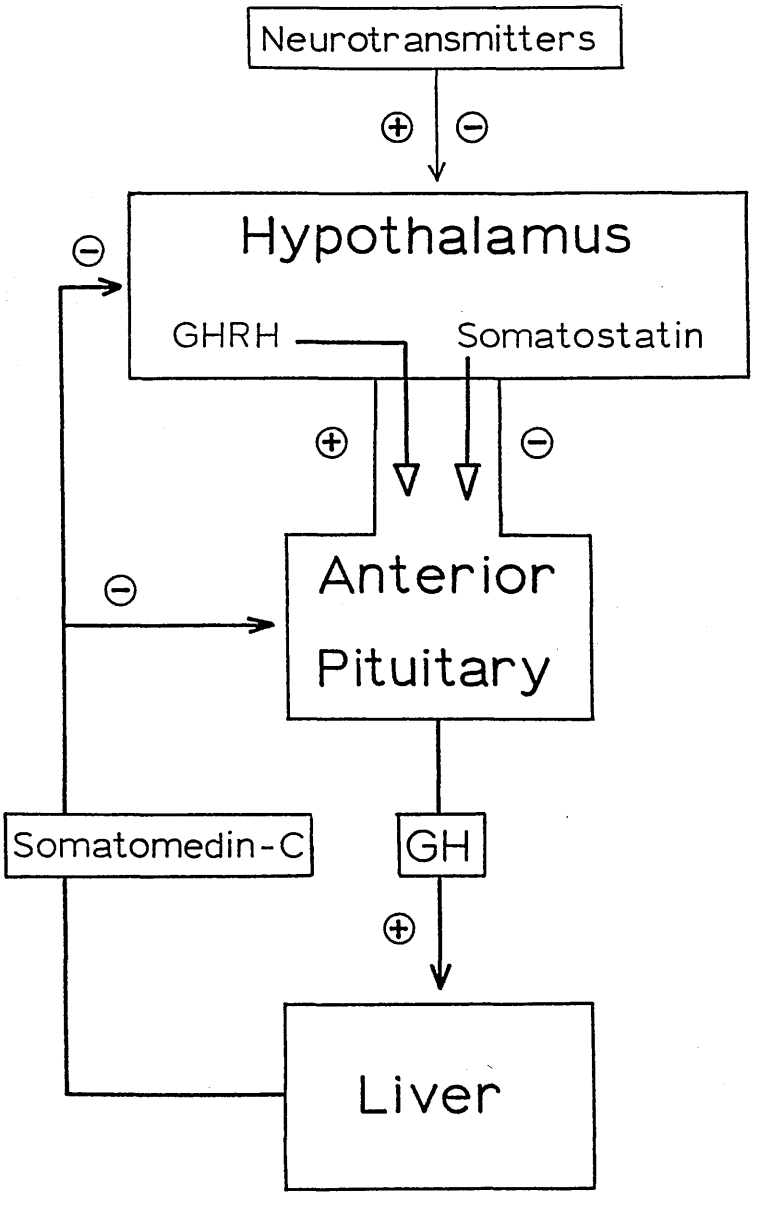
Control of GH secretion

GH is secreted episodically with most of the release occurring during sleep. Hypoglycaemia and exercise are strong stimuli to GH release and the sites at which glucose deprivation operates were shown to be in the lateral hypothalamus (Himsworth et al, 1972). Glucose administration and free fatty acids suppress GH secretion whereas several amino acids stimulate GH secretion (Knoff et al, 1965). The hypothalamic regulation of GH appears to be predominantly under the control of GHRH, with the inhibitor somatostatin possibly acting as a paracrine agent (Belchetz, 1984), (Fig 4). Pharmacological experiments also suggest that several neuropeptides influence the release of GH, with opioids, VIP and bombesin stimulating release, whereas substance P inhibits release (Jansson et al, 1985). Hypothalamic neurotransmitters may also alter GH secretion, by affecting the release of GHRH or somatostatin in the hypothalamus. Possible roles have been suggested for noradrenaline, dopamine, serotonin, GABA and acetyl choline (Delitala et al, 1987).

GH secretion after injury

GH levels increase shortly after injury and fall rapidly towards normal over 24 hours, even in patients with serious injuries (Carey et al, 1971; Frayn et al,

Figure 4 Central Control of GH Secretion



1984 b). Induction of anaesthesia does not appear to have an effect on GH levels (Noel et al, 1972) but a significant elevation occurs shortly after the commencement of surgery (Ross et al, 1966; Charters et al, 1969; Newsome and Rose, 1971; Noel et al, 1972; Wright and Johnston, 1975; Hagan et al, 1980; Traynor and Hall, 1981; Sowers et al, 1983; Lacoumenta et al, 1987). The levels begin to fall during surgery (Charters et al, 1969; Lacoumenta et al, 1987) and are often normal on the first post-operative day (Charters et al, 1969; Noel et al, 1972). The GH elevation was not correlated to the severity of operation, the anaesthetic agents or the age or sex of the patients (Charters et al, 1969). In patients with burns GH was usually within the normal range (Batsone et al, 1976; Popp et al, 1977; Dolecek et al, 1979; Balogh et al, 1984), although no samples were taken within 2 days of injury. One study reported raised values several weeks after burn injury (Wilmore et al, 1975).

There have been two studies examining the GH response after head injury. Rudman et al (1977) found no elevation in GH levels and no relationship with severity of injury. However as his subjects (7 in total) were not studied until day 6 a rise in GH may well have been missed. King et al (1981) studying a much larger group of subjects (29) investigated GH levels 3-5 days after injury for 1 month. He confirmed Rudman's findings demonstrating that GH levels were not significantly different from controls during the period

of his study and there was no relationship to the severity of injury. However he did demonstrate a significant elevation in GH in 3 of 6 subjects studied immediately after admission. Furthermore during the first 2 weeks after injury there was a paradoxical GH rise in response to intravenous glucose, which was more pronounced with increasing severity of injury, and which the authors suggested might be due to transient hypothalamic dysfunction.

Role of GH after injury

Growth hormone, like adrenaline, cortisol and glucagon is one of the counter-regulatory hormones, which respond to hypoglycaemia and play a role in maintaining euglycaemia. They are all elevated after injury and it has been suggested that they are responsible for the general catabolic state with stimulation of lipolysis, glycogenolysis and gluconeogenesis. However the increased levels in injured patients are dissociated from the catabolic changes by several days (Frayn et al, 1984 b) and although adipose tissue lipolysis may be stimulated by GH in vitro (Fain, 1980) and the high GH levels after injury may be sufficient to stimulate lipolysis, it has been shown that the early metabolic responses are very similar in man and rat (Heath, 1985), the latter being a species in which GH secretion is suppressed by stress and injury (Barton, 1977).

As most of the metabolic effects of GH are mediated by the somatomedins, which are a group of peptides synthesised by the liver in response to GH, they have been studied after injury (Frayn et al, 1984 b). Somatomedins are generally anabolic with effects on muscle protein metabolism (Salmon and Duvall, 1970; Uthne et al, 1974) and on whole body growth (Van Buul-Offers et al, 1979) and are involved in cartilage proliferation (Sevitt, 1980). Therefore the relative catabolic response after injury could be due to a depression of the somatomedin levels. Levels were found to be low 2-3 days after injury and in patients with burn injuries the duration of the depression was strongly correlated with the size of the burn (Coates et al, 1981). However in trauma patients the low levels bore no relationship to the catabolic response to injury, which was maximal at about one week (Frayn et al, 1984). Somatomedin activity was strongly correlated with plasma insulin, suggesting that this was a more important influence than GH after trauma (Frayn et al, 1984).

Summary

GH levels rise during surgery but rapidly return to normal. Two studies following head injury did not examine GH levels in the early phase after injury in sufficient numbers to determine if this also happens after head injury. One of these studies did demonstrate a central defect in GH control at a later stage after

injury. A role for GH in the general catabolic state after injury is uncertain.

PROLACTIN

Control of prolactin secretion

Prolactin is under tonic inhibitory control by the hypothalamus and the major prolactin inhibitory factor is dopamine (MacLeod, 1976). Direct evidence to support this has been produced in primates by Neill et al (1981) who showed that intravenous infusion of dopamine, to reproduce stalk blood levels, caused significant inhibition of prolactin secretion in both intact and stalk-transectioned animals. Endogenous opiates may modulate prolactin secretion as administration of exogenous opiates stimulates prolactin release (Grossman et al, 1981). Although the opiate receptor antagonist naloxone had no effect on resting prolactin levels (Grossman et al, 1981) it did reduce the rise in prolactin following surgery (Pontiroli et al, 1982) suggesting that opiates may be involved in the control of the prolactin response to stress. There is physiological and anatomical evidence to suggest that opiates affect prolactin by acting upon hypothalamic dopaminergic neurons (Fuxe et al, 1981). TRH stimulates prolactin release when administered exogenously but the physiological role of endogenous TRH in the secretion of prolactin remains uncertain (Franks, 1979). Various neurotransmitters such as VIP, CCK, serotonin and GABA may modulate prolactin secretion but their role appears minor in relation to dopaminergic control. In addition prolactin appears to

be able to regulate its own secretion through a short loop feedback, whereby prolactin has a direct action on hypothalamic dopamine turnover increasing the amount of dopamine available to the pituitary (Scanlon et al, 1981).

Prolactin secretion after injury

Prolactin levels have been found to increase following physical or emotional stress (Reichlin, 1981) but the exact stimuli and pathways controlling release of prolactin after these stresses are unknown. It has been suggested that stress either reduces the release of hypothalamic dopamine or increase the availability of factors that stimulate prolactin release, but as yet the mechanism is unknown (Gann and Lilly, 1984).

Operations performed under general anaesthesia produce an increase in prolactin which begins after induction but before skin incision, with the peak values occurring during the operation (Noel et al, 1972; Sowers et al, 1977; Hagan et al, 1980; MacFarlane and Rosin, 1980; Pontiroli et al, 1982). Female subjects have a greater rise in prolactin than male subjects (Noel et al, 1972). The rise in prolactin was blocked in patients having epidural analgesia suggesting that neurogenic stimuli are important in stimulating prolactin release (Hagan et al, 1980). Noel et al (1972) demonstrated that less invasive procedures such as gastroscopy and proctoscopy produced smaller increases in prolactin. Chest wall injury and surgical

procedures to the chest wall also produce elevations in prolactin level and can be associated with galactorrhoea (Morley et al, 1977; McFarlane and Rosin, 1980). The raised prolactin levels appear relatively short-lived and within 48 hours of thoracotomy the mean levels were not significantly elevated from the pre-operative levels (McFarlane and Rosin, 1980). The one study which examined prolactin levels after head injury found that 3 out of 6 patients had elevated values during the 72 hours of the investigation (King et al, 1981). One recent study reported that burn injuries produce a marked elevation in prolactin which is related to the severity of the injury and can be sustained for at least 4 weeks (Brizio-Molteni et al, 1984), but other studies have observed normal (Balogh et al, 1985) or reduced (Popp et al, 1977) prolactin concentrations after burns.

Role of prolactin after injury

Although prolactin is considered to be a stress hormone (Buckingham, 1985) its role in the body's response to trauma has yet to be defined. As yet the only function ascribed to this hormone in man is its contribution to lactation (Belchetz, 1984).

Summary

Prolactin levels are increased after all forms of injury and are greater in female subjects. Levels begin

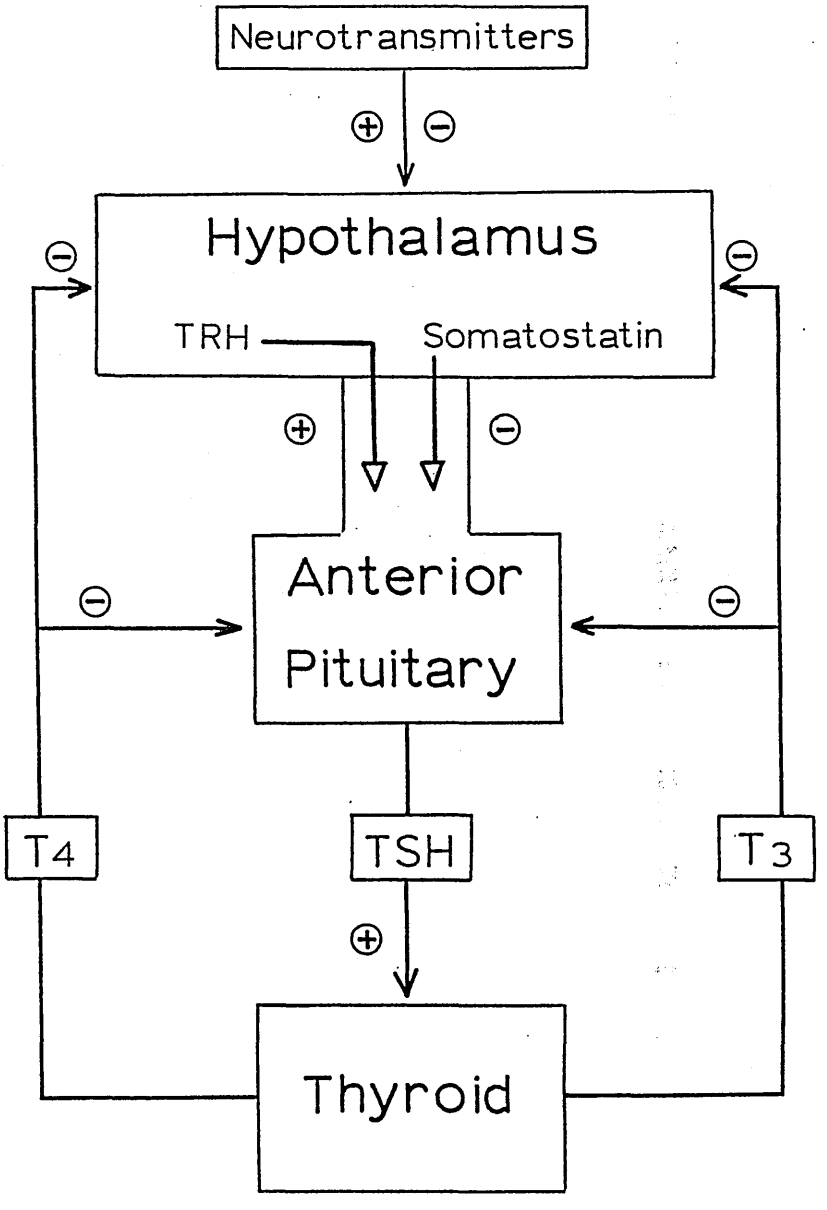
to rise during induction of anaesthesia and reach there peak intra-operatively, with a rapid return to normal. A small study in head-injured subjects found elevated levels within 72 hours of injury in 3 of 6 subjects. The role of prolactin in the stress response is unknown.

THE THYROIDAL AXIS

The control of TSH secretion

The hypothalamic control of TSH secretion is dependent on two neuropeptides, TRH and somatostatin. TRH is secreted by the hypothalamic neurons into the hypophyseal portal system and stimulates TSH release. Animal experiments in which TRH antiserum and TRH antibodies were administered have shown that thyroid function declines, confirming that TRH is important for the maintenance of normal thyroid function (Fraser and McNeilly, 1982). Somatostatin may be a physiological inhibitor of TSH release as somatostatin infusion lowers the elevated basal TSH level in patients with primary thyroid failure (Lucke et al, 1975), suppresses the TSH response to TRH (Siler et al, 1974) and abolishes the nocturnal elevation in basal TSH values (Weeke et al, 1975) (Fig 5). Dopamine also has an inhibitory role in the control of TSH secretion in man (Scanlon et al, 1980) and in rats there is a striking similarity between the inhibition of TSH and prolactin by dopamine (Foord et al, 1983). The neurotransmitter modulation of TRH is poorly documented but it appears that serotonin (Smythe et al, 1982) and noradrenaline may be stimulatory (Belchetz, 1984). Our finding that TSH is secreted in a pulsatile fashion (Clark et al, 1986 and 1987), which was subsequently confirmed by others (Greenspan et al, 1986) suggests that, as for

Figure 5 Central Control of the Thyroidal Axis



GnRH, there may be a hypothalamic pulse generator controlled by neuronal input from higher centres.

Thyroid hormones have a negative feedback action on the thyrotroph and it appears to be nuclear T3 which has the most important effect on pituitary TSH secretion (Larsen, 1982; Belchetz, 1984), such that nuclear binding of T3 and pituitary TSH secretion show a direct inverse relationship (Silva and Larsen, 1977). As the pituitary has a greatly enhanced ability, compared with the liver or kidney, to yield T3 from circulating T4, the thyroid status as viewed by the thyrotroph is more influenced by circulating T4, although TSH secretion is directly regulated by intranuclear T3 (Belchetz, 1984).

The thyroidal axis and injury

There have been many studies of thyroid function after injury or serious non-thyroidal illness and the pattern of abnormalities has been termed the sick euthyroid syndrome (Wartofsky and Burman, 1982). The typical alterations in the thyroidal hormones T4 and T3 are well established but there has been considerable change in the interpretation of the TSH response to critical illness in the last 1-2 years, with the development of TSH assays with improved sensitivity and lower limits of detection.

A low T3 is commonly found in intensive care patients (Zaloga and Chernow, 1985) and is seen in a variety of clinical conditions including liver disease,

sepsis, neoplastic disorders, renal disease, burns, surgery, myocardial infarction and starvation (Kirby et al, 1973; Portnay et al, 1974; Brandt et al, 1976; Popp et al, 1977; Adami et al, 1978; Becker et al, 1980; Smeds et al, 1981; Wiersinga et al, 1981; Wartofsky and Burman, 1982; Balogh et al, 1984; Zaloga and Chernow, 1985; Semple, 1986). T3 begins to fall immediately after injury and remains depressed for a few days after surgery, a few weeks after major injury and even longer after severe burns.

This occurs because the majority of T3 is derived from the peripheral conversion of T4, a process which is reduced in ill patients (Carter et al, 1976). There is an associated increase in the metabolically inactive reverse T3 as a result of decreased rT3 degradation rather than increased production (Chopra, 1976). There is in vitro evidence suggesting that the same 5'-deiodinase enzyme system may convert T4 to T3 and rT3 to its metabolites (Chopra et al, 1978). Therefore inhibition of this enzyme could account for the observed changes.

In more severely ill patients both T4 and T3 concentrations are low and it has been shown that after acute trauma (Philips et al, 1984) and during critical illness (Slag et al, 1981) low T4 is associated with a poor prognosis. One of the explanations for the low T4 is that it is displaced from TBG by binding inhibitors, which have been identified in the serum of critically ill patients (Oppenheimer, 1982), but there is also

decreased T4 secretion from the thyroid gland (Kaptein et al, 1982) and an accelerated T4 disposal resulting in a reduced half-life (Gregerman and Solomon, 1967; Kaptein et al, 1982). It has been suggested that the binding inhibitors may leak out of extrathyroidal tissue into the circulation when the integrity of the tissue is compromised during severe illness (Chopra et al, 1979; Chopra et al, 1982).

The binding inhibitors can interfere with many of the kit methods available for measuring the free hormones (Chopra et al, 1980). Wehmann et al recently reported reduced levels of free T4 measured by equilibrium dialysis (1985), although previous reports have found the free T4 to be normal or high and free T3 concentrations normal or low (Chopra et al, 1974; Chopra et al, 1980).

Infrequently a high total T4 occurs in critically ill patients and is due to an increase in TBG. There may be an associated increase in T3 but free T4 is usually normal (free T3 is reduced due to a reduction in the peripheral conversion of T4 to T3) (Zaloga and Chernow, 1985).

The tissue levels of thyroid hormones have been examined in a few studies. Tissue uptake may be impaired by binding inhibitors (Oppenheimer et al, 1982), although intracellular red blood cell levels of T4 were normal in a few patients with a reduced serum T4 (Mendel and Cavalieri, 1984). A low tissue concentration of T3, with a normal tissue concentration

of T4, was found in patients dying of severe chronic illness (Reichlin et al, 1973). However one study in which tri-iodothyronine was administered to severely ill burned patients who had low concentratons of thyroidal hormones revealed no effect on survival (Becker et al, 1982).

Until 1985 most reports and review articles had stated that the serum TSH level was normal in critical illness and the TSH response to TRH was also normal (Gann and Lilly, 1984). However with the development of a more sensitive TSH assay Wehmann et al (1985) reported that in patients who became seriously ill after marrow transplantation for haematologic malignancy a fall in TSH to subnormal levels usually preceded the decrease in T4. When recovery occurred TSH and T4 increased concomitantly. In a further study Hamblin et al (1986) noted that in patients with hypothyroxinaemia due to critical illness there was a close and consistent temporal relationship between TSH and T4 during the recovery phase, suggesting that TSH may have an essential role in the return of T4 to normal during recovery. Thus it has been suggested that severe illness can inhibit TSH secretion and along with the accelerated disposal of T4, contributes to the fall in T4 concentration (Wehmann et al, 1985). Additional evidence for hypothalamo-pituitary dysfunction in this group has been demonstrated by an impaired TSH response to TRH in hypothyroxinaemic critically ill patients (Vierhapper et al, 1982). Furthermore after

demonstrating that TSH was released in a pulsatile fashion in healthy individuals (Clark et al, 1986) we have demonstrated that in patients with renal failure pulsatile release is abnormal and there is loss of the normal evening rise in TSH (Wheatley et al, 1987).

The role of the thyroidal axis after injury

As TSH levels do not rise above normal during the low T3 and T4 states of critical illness it has been concluded that an overall euthyroid status is present (Oppenheimer, 1983), thereby implying that the thyroidal axis is not involved in the response to injury. However the recently demonstrated reduced pituitary TSH secretion in critical illness (Wehmann et al, 1985; Hamblin et al, 1986) and the impaired pituitary responsiveness to TRH (Vierhapper et al, 1982) indicate that secondary or tertiary hypothyroidism is occurring in response to severe injury.

Summary

Following injury thyroidal hormone concentrations fall, with T3 frequently subnormal. Low T4 levels occur during severe injury or illness and are associated with a poor prognosis. Recently workers have demonstrated that TSH levels are also subnormal, implying that secondary or tertiary hypothyroidism is present. However a study in which tri-iodothyronine was given to

severely burned subjects demonstrated no effect on survival.

THE GONADAL AXIS

Control of gonadotrophin secretion

Gonadotrophin secretion is controlled by the hypothalamic secretion of GnRH and the negative feedback effects of the gonadal steroids. Oestrogens can also elicit pre-ovulatory LH and FSH surges. Both FSH and LH are secreted in a pulsatile fashion from the anterior pituitary and in women the frequency and amplitude of LH pulses varies with the stage of the menstrual cycle (Knobil, 1980). There is considerable evidence that LH pulses are the direct result of GnRH pulses secreted from the median eminence into the hypophyseal portal blood. Clarke and Cummins (1982) sampled GnRH in the portal blood and LH in the peripheral blood and demonstrated a one-to-one relationship between large GnRH and LH pulses.

Recordings of multi-unit activity in the mediobasal hypothalamus have demonstrated that neural activity can be correlated with pulsatlie release of LH (Thiery and Pelletier, 1981; Kawakami et al, 1982; Wilson et al, 1984), indicating that there is a neural pacemaker governing the activity of the GnRH neurons. Hypothalamic deafferentation experiments suggest that the site responsible for generating the rhythmic activity lies in the mediobasal hypothalamus in the monkey (Krey et al, 1975), possibly within the arcuate nucleus (Soper and Weick, 1980).

Neuroanatomical studies have demonstrated that the main sites of GnRH neurons are in the preoptic/septal region of the brain and the mediobasal hypothalamus (Hoffman, 1983) and both these regions receive noradrenergic innervation (Lindvall and Bjorklund, 1974; Day et al, 1980; Berk and Finkelstein, 1981). It has been shown that alpha 1 adrenergic blocking agents inhibit LH pulsatility in monkeys (Bhattacharya et al, 1972) and, along with dopamine blockers, they inhibit the multi-unit activity in the medio-basal hypothalamus, which is correlated with LH pulses (Kaufman, 1981). The catecholamine influence on GnRH pulsatility was further investigated by Clifton and Sawyer (1979) who transected the ascending noradrenergic pathways in the rat and found that cyclicity was minimally effected, although anovulation occurred in some animals if noradrenaline synthesis was also blocked. They concluded that noradrenergic inputs are modulatory rather than mandatory.

Several neuropeptides have been found to influence LH pulsatility, with opioid peptides having the greatest effect. Treatment with the opioid antagonist naloxone leads to increases in LH secretion in men and women (Quigley and Yen, 1980; Ellingboe et al, 1982) and is associated with an increase in LH pulse frequency and in some cases amplitude (Moult et al, 1981; Ellingboe et al, 1982). The effects of naloxone are blocked by GnRH antagonists (Blank and Roberts, 1982), so it has been postulated that endogenous

opioids inhibit GnRH release. B endorphin is thought to be the most likely candidate and it is located in the arcuate nuclues of the hypothalamus (Grossman, 1983). There is evidence supporting an adrenergic or noradrenergic link with the opioid peptides and it seems that opioid inputs can modulate the catecholamine inputs to the GnRH system either at the level of the GnRH cell bodies or the GnRH terminals in the median eminence (Kalra, 1986). The neuropeptides substance P, neuropeptide Y and vasoactive intestinal peptide have also been found to affect gonadotrophin secretion (Clarke and Cummins, 1987), although their precise roles have not yet been defined.

Testosterone secretion after injury

In the past 20 years it has become apparent that gonadal hormone concentrations fall to subnormal levels after severe stress. Subjects have been found to have reduced levels after various major medical insults including myocardial infarction (Wang et al, 1978 a; Woolf et al, 1985), surgery (Charters et al, 1969; Aona et al, 1972; Nakashima et al, 1975; Wang et al, 1978 b), burns (Dolecek et al, 1979; Vogel et al, 1985), respiratory insufficiency (Semple et al, 1981; Goussis et al, 1983), acute renal disease (Handelsman, 1985), CVA (Woolf et al, 1985) and head injury (Rudman et al, 1977; Woolf et al, 1985; Woolf et al, 1986). The mechanisms responsible for this reduction have not yet been elucidated. In order to determine whether

abnormalities in the central control of the gonadal axis could be responsible many studies have also examined the gonadotrophin levels, and in a few cases the LH and FSH response to stimulation with GnRH (Rudman et al, 1977; Woolf et al, 1985). There is general agreement that testosterone decreases by 40-70 % within 24 hours of these traumatic events (Goussis et al, 1983; Woolf et al, 1985). Recovery back to normal levels differs between the illnesses, with myocardial infarction and surgery having shorter recovery times, usually within 1 week (Aono et al, 1972; Aono et al, 1976; Wang et al, 1978 a; Wang et al, 1978 b; Woolf et al, 1985). The severity of the injury appears to be related to the extent of the fall in testosterone. Nakashima et al (1975) demonstrated that major surgical procedures produced a greater reduction in testosterone than minor surgical procedures and Woolf et al (1986) demonstrated that after head injury there was a smaller fall in testosterone in patients with less severe injuries.

The effect of injury on gonadotrophin secretion in men

As gonadal hormones are primarily under the control of the hypothalamus and pituitary, many studies have investigated gonadotrophin levels but with conflicting results. An increase in LH secretion has been reported shortly after commencing operation by some authors (Aono et al, 1972; Nakashima et al, 1975; Aono et al, 1976), whereas other authors have reported

no perioperative changes in LH concentration (Charters et al, 1969; Oyama et al, 1979). During the first and second post-operative days the LH level has fallen in some reports (Chaters et al, 1969; Aono et al, 1972; Hagen et al, 1980), although in one study it was not significantly different from control values (Aono et al, 1976). FSH levels have been reported to fall after surgery (Woolf et al, 1985). An early increase in gonadotrophin levels with a subsequent significant decrease has also been reported after burn injury (Brizio-Molteni et al, 1984), although Dolecek et al (1979) reported that LH levels are elevated in 25 % of cases, normal in 31 % and low in 44 %. No changes were observed in LH and FSH after acute myocardial infarction in one study (Woolf et al, 1985), whereas Wang et al (1978 a) observed a significant increase in LH on day 4. Following head injury an initial elevation in FSH and LH (King et al, 1981; Woolf et al, 1986) has been observed. Subsequently the FSH and LH levels decreased significantly (Woolf et al, 1985; Woolf et al, 1986) with one study reporting subnormal levels (Rudman et al, 1977). Woolf et al (1985) also observed that the decrease in LH and FSH occurred after the decline in testosterone. Rudman et al (1977) and Woolf et al (1985) performed GnRH tests on a total of 9 head-injured patients who had been treated with dexamethasone and found the gonadotrophin responses to be normal. In patients with burns the response to GnRH was also reported to be normal (Dolecek et al, 1979;

Balogh et al, 1984). Interpretation of these studies would suggest that acute stress leads to a brief temporary increase in LH and possibly FSH secretion, with a subsequent reduction over the ensuing days, occasionally to subnormal levels.

Injury and gonadal axis dysfunction in women

There have been few studies on the effect of trauma on gonadotrophin and gonadal hormone concentrations in women and no systematic studies in different phases of the menstrual cycle have been performed. Woolf et al (1985) demonstrated that oestradiol levels began to fall within 24 hours of injury (either an intracranial vascular accident or a head injury) in women of reproductive age and continued to fall into the postmenopausal range. These changes were independent of the phase of the menstrual cycle and were accompanied by falling gonadotrophin levels. Postmenopausal women had a similar response to trauma but with a greater fall in gonadotrophin levels. The abnormalities persisted for 7 days in women of reproductive age and were not associated with any changes in sex hormone binding capacity. No other studies have reported oestradiol levels although two studies have reported a transient fall in LH levels 5-6 hours (Aono et al, 1976) and 9 hours (Hagan et al, 1980) after surgery, which had returned to normal by 24 hours (Hagan et al, 1980). Hagan also reported a transient fall in FSH which was also normal within 24

hours, although Aono reported no change. Abnormalities also occur after thermal injury, with severely burned women failing to ovulate for several months after injury (Diem et al, 1979). In postmenopausal women a hypothalamo-pituitary defect is suggested by the fall in gonadotrophin concentration during severe illness (Warren et al, 1977), surgery (Aono et al, 1976) and head injury (Woolf et al, 1985).

Mechanisms responsible for gonadal axis dysfunction

It has been suggested that the fall in testosterone may be due to changes in SHBG and albumin following trauma and that the free or biologically active testosterone is normal or increased. Goussis et al (1983) investigated 10 critically ill patients and found that sex hormone binding globulin (SHBG) increased by 35 % and albumin decreased by 24 %. Unlike the thyroidal axis, where inhibition of thyroid hormone binding to TBG occurs, an increase in serum binding of testosterone by SHBG was observed. The free (dialyzable) testosterone fraction was not significantly changed, indicating that these patients are truly hypogonadal. The authors suggested that the low testosterone concentration appears to reflect decreased testosterone secretion, as the changes in binding proteins would, if anything, decrease testosterone clearance. A second study (Gray et al, 1978) in male rats exposed to chronic stress demonstrated that normal male rats had a reduction in

testosterone, whereas levels did not fall in castrated testosterone-treated animals. This confirmed that the suppression must result from a reduction in testosterone secretion.

Most studies agree that the gonadotrophin concentrations are inappropriately low for the level of gonadal hormone indicating that there is disruption of the normal feedback mechanism. However as it has been shown that the changes in gonadotrophin concentration occur after the fall in gonadal steroids (Woolf et al, 1985) and in other cases, such as myocardial infarction, there was no fall in gonadotrophin concentration (Woolf et al, 1985), it is apparent that the hypogonadism is not secondary to the absolute level of gonadotrophins. This does not exclude a central cause for the hypogonadism as possible abnormalities in pulsatile secretion of the gonadotrophins or alterations in the ratio of bioactive to immunoactive LH have not been investigated.

Other mechanisms have been suggested which may operate at either the hypothalamo-pituitary or gonadal level. As cortisol is elevated in these subjects it has been proposed as a possible mediator of the gonadal axis abnormalities. Although most studies on normal volunteers have shown a suppression in testosterone after administration of ACTH or exogenous glucocorticoids there is disagreement as to whether this is a central or direct gonadal effect (Sakakura et al, 1975; Doerr and Pirke, 1976; Cumming et al, 1983).

However some studies have reported no effect (Smals et al, 1974) or a stimulatory effect (Kirschner et al, 1965) on gonadal hormones. Furthermore head-injured patients treated with dexamethasone had results comparable to those who did not receive any glucocorticoids (Woolf et al, 1985) and similar observations have been reported in surgical patients (Nakashima et al, 1975). Gray et al (1978) demonstrated that stressed adrenalectomised rats had a fall in testosterone, whereas unstressed adrenalectomised rats had no fall, which they took to indicate that the pituitary-adrenal axis did not mediate the changes in the gonadal axis.

The sympathetic nervous system is activated by severe injury and particularly by traumatic brain injury (Clifton et al, 1981) and it is known that infusion of adrenaline decreases both testosterone production and concentration (Levin et al, 1967), whereas dopamine suppresses levels of gonadotrophins but not testosterone (Huseman et al, 1980; Travaglini et al, 1981; Nakagawa et al, 1982; Sowers et al, 1983). Therefore Woolf et al (1986) examined the possibility of catecholamine mediation of the changes in gonadal hormone concentration. A highly significant inverse correlation was found between admission noradrenaline, adrenaline and the day 4 testosterone concentration. As mildly injured patients with small elevations of catecholamines were found to have no change in testosterone, despite a significant fall in LH, the

authors suggested that any catecholamine effect was probably on testicular secretion of testosterone.

Another central mechanism which could produce the observed changes is dependent on the opioidergic system. Opioids are an important modulator of the hypothalamic pulse generator (Moult et al, 1981; Ellingboe et al, 1982) and increased opioidergic tone which occurs after stress could result in loss or decrease of gonadotrophin pulsatility.

Summary

Following injury there is a fall in testosterone levels in male subjects and oestradiol levels in female subjects. The extent of the fall in testosterone is related to the severity of the injury. Changes in gonadotrophin levels after injury have differed between studies. However it appears that there may be a transient increase in their concentrations shortly after injury, followed by a reduction, occasionally to subnormal levels.

The mechanism responsible for the fall in gonadal steroid concentration is unknown. Different groups have suggested that, after injury, increased levels of glucocorticoids, catecholamines or opioids, may produce either peripheral or central gonadal dysfunction.

ENDOCRINE STUDIES PERFORMED AFTER HEAD INJURY

There have been few studies of endocrine function following head injury and most workers have investigated only a small number of subjects. Hormones have been measured at a variable time after injury with dynamic tests performed infrequently. All the studies have concentrated on the hormonal changes on admission and shortly afterwards with no long term follow up.

In 1977 Rudman et al reported both hypothyroidism and hypogonadism in 7 male patients following major head injury. Thyroidal dysfunction (decreased levels of T4, T3, fT4 & TSH) and gonadal dysfunction (decreased levels of testosterone, FSH & LH) developed after 6-7 days coma and resolved after regaining consciousness. The GH, PRL and cortisol concentrations did not differ from normal, although cortisol levels did became elevated when therapy with dexamethasone was stopped. As the TRH and GnRH tests were normal but the the basal TSH and gonadotrophin concentrations were reduced the abnormality was considered to be at the hypothalamic level. Clinicians were advised to monitor head injury patients for myxoedema coma.

A small study of hypothalamo-pituitary function was reported by King et al in 1981 in which the diurnal variation in GH, PRL, TSH, FSH and LH were investigated in 6 patients by analysing samples taken from admission to the third day at four hourly intervals. In addition the GH response to intravenous glucose was determined.

During the four hourly sampling GH, PRL, LH and FSH were elevated in 3 of the 6 patients studied. However the hormone elevations were not in the same 3 patients. In contrast to Rudman's study the only consistent finding was a normal TSH concentration in all 6 patients. There was no predictable hormone pattern and no relation to the degree of injury or time after injury. Further evidence of hypothalamo-pituitary dysfunction was demonstrated by a paradoxical increase in GH during an intravenous glucose load, in severely injured patients.

Considerably more information is known about the cortisol response in head injury. King et al (1970) studied 13 patients, again taking four hourly samples from admission to 36 hours. The cortisol level was found to be elevated and significantly greater than a control group of patients who had samples taken after operations (laminectomy). Loss of circadiam rhythm persisted in patients with prolonged coma, even when cortisol levels had returned to within normal limits.

In a larger study of 49 patients Steinbock and Thompson (1979) confirmed the post-injury elevation in cortisol with loss of circadian rhythm. In addition he reported a correlation with the severity of the head injury (as determined by the duration of coma) and there was a trend suggesting that middle fossa basal skull fractures predisposed to cortisol abnormalities. In 6 patients hypercortisolaemia persisted for greater than 1 week. In a further 6 patients dexamethasone was

found to partially supress the elevated levels, suggesting that hypercortisolaemia after head injury is related to an alteration rather than an abolition of the normal feedback mechanism.

Two recent papers by Woolf et al (1985 and 1986) have presented further data on the gonadal axis, confirming the hypogonadism observed by Rudman. The first study was designed to examine the effect of head injury, myocardial infarction, surgery and intracranial vascular accidents on the gonadal axis. The 17 men and 5 women with traumatic head injury were found to have the largest fall in testosterone and oestradiol respectively, when compared to the other 3 groups. Although significant decreases in LH and FSH were found these occurred after the decline in gonadal steroids. The gonadotrophin responses to GnRH in the 4 patients tested (3 were receiving dexamethasone) and the SHBG concentrations were within normal limits. The authors concluded that as LH and FSH were inappropriately low for the level of testosterone and oestradiol, their patients had developed secondary pituitary insufficiency and because the pituitary gonadotropes response to GnRH had been normal in the 4 patients tested, they concluded the abnormality must be at the hypothalamic level.

In his second paper Woolf (1986) observed that the magnitude of the hormonal dysfunction was dependent upon the severity of the neurological insult, with a 53 % fall in testosterone between admission and day 4 in

severely injured patients, compared to a 25 % fall in the less severely injured.The testosterone precursors, 17 OH progesterone and DHEA sulphate, were also reduced by day 4. Although the LH and FSH concentrations were significantly reduced from elevated admission levels, only the less severely injured had subnormal LH levels. In all patients the noradrenaline and adrenaline concentrations were elevated on admission and a highly significant negative correlation was found between admission noradrenaline and adrenaline levels and the day 4 testosterone. Thus the authors concluded that the sympathetic nervous system might be mediating the gonadal axis dysfunction.

Summary

Hypercortisolaemia is a freqent finding after head injury with disruption of the normal circadian rhythm. Transient hypogonadotrophic hypogonadism, possibly of hypothalamic origin, is also well recognised. Findings in the thyroidal axis are more varied with one author reporting hypothalamic hypothyroidism with subnormal TSH values in 7 patients, while another reported completely normal TSH values in 6 patients. Prolactin and growth hormone have only been examined in one small study of 6 patients, in which 3 cases were found to have elevated values.

INVESTIGATION OF HYPOTHALAMO-PITUITARY HYPOFUNCTION

During the last 2 decades considerable advances have been made in diagnostic endocrinology with the development of radioimmunoassays for pituitary hormones. These assays are cheap, rapid and reliable, but many of them are less sensitive at low hormone concentrations and unable to detect subnormal values. Thus clinical hypopituitarism can occur with basal hormone levels still within the normal range of the assay and paradoxically, as some pituitary hormones (eg GH) are secreted episodically, normal individuals may have undetectable levels at certain times during the day. To overcome these difficulties dynamic tests capable of quantifying pituitary hormone reserve were developed. The isolation and synthesis of the hypothalamic releasing factors thyrotrophin releasing hormone (TRH, a tripeptide) in 1969 (Boler et al, 1969) and luteinising hormone releasing hormone (GnRH, a decapeptide) in 1971 (Matsuo et al, 1971) provided specific tools to investigate their respective pituitary axes. Since their synthesis and commercial availability they have been used in combination with insulin as a complete test of hypothalamo-pituitary reserve (Harsoulis et al, 1973).

Insulin combined test

This test is performed over 2 hours and consists of the intravenous administration of insulin (0.05-0.15

U/kg), TRH (200 ug) and GnRH (100 ug). Assuming adequate hypoglycaemia is achieved (blood glucose < 2.1 mmol/L) both GH and ACTH release will be stimulated from the anterior pituitary. Since the cortisol response parallels the ACTH response and its assay is more reliable and cheaper, cortisol is usually measured in place of ACTH.

It was hoped that the hypothalamic releasing factors in the combined test (triple bolus test) might be able to distinguish between hypothalamic and pituitary disease but this has not been the case. An initial report by Faglia et al in 1973 suggested that hypothalamic hypothyroidism was characterised by a delayed, prolonged and exaggerated TSH response to TRH, whereas pituitary dependent hypothyroidism led to a subnormal or absent TSH response to TRH. However subsequent workers (Tunbridge et al, 1973) have shown that while a flat TSH response indicates pituitary disease with a high degree of probability, normal or exaggerated TSH responses can occur in both pituitary and hypothalamic disease. The newer TSH assays are capable of defining a lower limit of the normal range and are gradually replacing the TRH test, which has rarely been complicated by pituitary apoplexy (Lever et al, 1986).

GnRH is also unable to distinguish between hypothalamic and pituitary disease since disorders of either centre produces a flat gonadotrophin response to stimulation. The loss of endogenous GnRH pulsatility in

hypothalamic disorders results in decreased synthesis of LH and FSH, so that even with an intact pituitary a subnormal response occurs. It has been possible to overcome this problem by pre-treating the patients with timed pulses of GnRH, so that despite hypothalamic disease pituitary synthesis of gonadotrophins is re-established, resulting in a detectable response to stimulation.

The standard method for assessing the hypothalamo-pituitary axis has been the insulin tolerance test but it cannot be used in certain circumstances; firstly in patients aged more than 50 years because of the increased risks of myocardial ischaemia and secondly in epileptic patients. Particular care must be taken if the test is carried out in patients with frank hypopituitarism since severe hypoglycaemia, coma and death can ensue. Medical supervision is required throughout the test because of the risk of unconsciousness and a supervised meal is necessary on completion of the test. Occassionally patients report that the test was unpleasant because of drowsiness, sweating, palpitations and hunger. However if all the precautions are strictly observed the test can be performed routinely on an out-patient basis with minimal risk.

Corticotropin and growth hormone releasing factors

The next significant advance occurred in 1981 when Vale et al (1981) characterised a 41 amino-acid

peptide, corticotropin releasing factor (CRF), which is considered to be one of the principal releasing factors for ACTH in man. Orth et al (1983) observed that the rise in ACTH following CRF administration is less than that after insulin induced hypoglycaemia, and suggested that other substances, such as vasopressin, must also contribute to ACTH release. Nonetheless CRF is considered very useful in the evaluation of patients with suspected ACTH deficiency. It has been reported that pituitary disease typically results in an absent or subnormal ACTH response to stimulation, whereas hypothalamic disease produces an exaggerated ACTH response to CRF (Tsukada et al, 1984). This augmented response has been ascribed to the low plasma concentration of glucocorticoid which is known to suppress the pituitary responsiveness to CRF. The authors concluded that the CRF test is a useful tool for evaluation of pituitary ACTH reserve and has diagnostic value in adrenocortical insufficiency due to hypothalamic and pituitary disorders.

In the CRF test 50-100 ug of CRF is administered as an intravenous bolus with ACTH and/or cortisol measured over the subsequent 2 hours, with the peak cortisol response occurring within 60 minutes.

In 1982 Guillemin et al (1982) and Rivier et al (1982) isolated 44 and 40 amino-acid residues of growth hormone releasing hormone (GHRH) from 2 pancreatic tumours in patients presenting with acromegaly. Subsequently it was found that only the first 29 amino-

acids are required for full agonist activity (Grossman et al, 1984). The GHRH test consists of the intravenous administration of 50-100 ug of the 29, 40 or 44 amino-acid residue with GH measured over the ensuing 2 hours. In healthy individuals the GH response is extremely variable, with a wide normal range (Grossman et al, 1984), and peak values are less than those after insulin-induced hypoglycaemia (Wakabayashi et al, 1986). In growth retarded children and adults attempts have been made to separate hypothalamic from pituitary causes, with an absent GH response typically occurring in pituitary disease (Grossman et al, 1984). Coincidental with the withdrawal of human growth hormone in 1985 GHRH was used therapeutically in a few centres in growth retarded children with a degree of success (Ross et al, 1986).

Combined releasing factor test

As all the pituitary axes could now be tested by the 4 releasing factors workers have recently reported on the anterior pituitary hormone responses to combinations of these factors in animals, healthy volunteers and patients with various pituitary disorders.

The first releasing factor combination study was carried out in rats (Wehrenburg et al, 1984) and it indicated that there was no direct interaction between the 4 releasing factors at the pituitary level. The authors concluded that any single or multiple impaired

hormone response would be due to single or multiple pituitary abnormalities, rather than due to interaction between the administered secretagogues.

The first study in humans (Sheldon et al, 1985) confirmed that there was no significant interaction and reported that the hormone response to the 4 factor combination was not statistically different from the hormone response achieved when the releasing factors were administered alone.

The second study (Holl et al, 1985) reported the hormonal increments to the releasing factor combination in 10 normal men and women and considered the test a valuable, physiological assessment of hypothalamo-pituitary function. The authors observed an increased and prolonged TSH rise and suspected augmentation of the TSH response to TRH by GHRH.

The next study (Looij et al, 1986) confirmed a significant potentiation of the TSH response to TRH by GHRH. However because there was no inhibition of hormone release it was thought that the releasing factor combination was a valuable test of anterior pituitary function.

A further study (Sandler et al, 1986) compared the hormonal responses to the 4 releasing factor combination plus arginine vasopressin with a conventional combined test using insulin together with TRH and GnRH. Both normal volunteers and patients with pituitary disorders were studied. No difference between the 2 tests was observed in the LH, FSH, TSH and PRL

responses to stimulation. Both the cortisol and GH responses to the releasing factor combination with vasopressin were significantly greater than those seen with insulin induced hypoglycaemia or the combined releasing factor test without vasopressin. Patients with pituitary hypofunction were distinguished by both tests. As most peak hormone responses occurred within 60 minutes of administration of the releasing factors it was suggested that the test could be achieved using only basal, 30 and 60 minute samples. The authors concluded that the combined releasing factor test appeared to be a safe, rapid and useful test of anterior pituitary function.

In the 4 studies the dosage of TRH and GnRH was consistent (200 and 100 ug respectively). However in Sheldon's study (1985) CRF and GHRH were both administered at a concentration of 1 ug/kg, whereas in the other 3 studies 100 ug of each were used. The releasing factors were administered as successive 20 second intravenous infusions or at 2 and 3 minute intervals. Clinical effects of the releasing factor test included transient nausea, flushing, a feeling of warmth over the face and upper trunk, dysgeusia and urinary urgency. No symptoms persisted for more than 10 minutes and there was no effect on blood pressure or pulse rate. None of these side-effects were more severe or prolonged than what has already been reported for CRF (Orth et al, 1983), GHRH (Thorner et al, 1983) or TRH (Anderson et al, 1971).

As most of the patients in our study were critically ill at the time of initial investigations pituitary function had to be assessed using a test which was simple and practicable, had no deleterious effect on conscious level and no significant side-effects. The insulin combined test is contraindicated because hypoglycaemia could further impair consciousness, whereas the combined releasing factor test has no effect on conscious level, no serious side-effects and only requires 3 blood samples after administration of the releasing factors. The latter test was therefore used in this study. The disadvantage in using a multiple releasing factor stimulus is that it can only test the pituitary gland, whereas the insulin component, in the insulin combined test, assesses both the hypothalamus and pituitary. This differance in site of action may be important as dissociation between the two kinds of tests has been noted, not only in patients with primary hypothalamic disorders but also in those with large pituitary tumours with suprasellar extensions, which cause disturbance of the portal vascular link (Lytras et al, 1984). However in patients with hypothalamic hypoadrenalism it is likely that the pituitary-adrenal response to CRF would be subnormal, the basal cortisol low and other endocrine deficits would be present.

ASSESSING BRAIN DAMAGE AFTER HEAD INJURY

Many factors affect the outcome after a major head injury including the patient's age and psychosocial status but the most important determinant is the degree of brain damage. As many British hospitals admit upto 1000 cases of head injury each year and upto 1 million cases present to Accident and Emergency Departments in the United Kingdom it is important to have a quick, reliable means of estimating the severity of brain injury (Jennett, 1979). Furthermore this must be assessed at an early stage after injury, so that patients who appear to be relatively mildly injured, but are at risk of developing early complications, or who appear severely injured but have the potential for recovery, can be identified quickly and appropriate therapeutic measures taken.

GLASGOW COMA SCALE

Since 1974 the most widely adopted method for estimating the severity of brain damage has been the Glasgow Coma Scale (Teasdale and Jennett, 1974). This scale defines the level of responsiveness in 3 modalities - eye opening, motor response and verbal response and by assigning numerical values to each parameter the score can be analysed statistically (Jennett et al, 1976). High numbers are used for normal responses and low for abnormal responses. Patients scoring 7 or less are in coma, those with 9 or more are

out of coma and about half of those with scores of 8 are in coma. Thus the coma scale is an index of the depth of coma and it has a continuous relationship with outcome (Fig 6). When comparisons were made between studies it was found necessary to standardise the time at which assessment was carried out and the best value within 24 hours was used (Jennett, 1979).

DURATION OF COMA AND POST-TRAUMATIC AMNESIA

Further indices of the severity of brain injury (and thus outcome) include the duration of coma and post-traumatic amnesia (PTA) (Jennett et al, 1976). In view of the practical difficulties involved in defining accurately the time at which a person has come out of coma it was decided not to attempt to record the duration of coma in this study. Furthermore it has been demonstrated that this parameter is less accurate at predicting outcome than PTA (Russell and Smith, 1961).

By assessing patient outcome after 6 months Jennett et al (1981) have shown that the length of PTA correlates well with the degree of eventual disability. Almost all patients with severe disability had a PTA of greater than 4 weeks and over 80 % of patients with a PTA of less than 2 weeks made a good recovery.

Figure 6 Glasgow Coma Scale

Eyes open		Motor response		Verbal response	
Spontaneous	4	Obeys commands	6	Orientated	5
To speech	3	Localises	5	Confused	4
To pain	2	Flexor withdrawal	4	Inappropriate words	3
Never	1	Abnormal flexion	3	Sounds only	2
		Extends	2	Nil	1
		Nil (flaccid)	1		

Score or sum = E + M + V = 3-15

C H A P T E R 2

SUBJECTS AND METHODS

Patients and Clinical Details

Releasing Factor Test

Hormone Analysis

Histopathological Study

Statistical Analysis

PATIENTS AND CLINICAL DETAILS

Sixty consecutive adult patients admitted with a major head injury were included in the study. A major head injury was defined as resulting in a period of unconsciousness followed by post-traumatic amnesia of greater than 24 hours duration (Russell and Smith, 1961).

Exclusion Criteria

1 No patients under the age of 16 were included in the study.

2 Patients who received treatment with methylprednisolone or dexamethasone (usually administered by a referring hospital) were not studied.

3. It was planned that patients with a history of endocrine disease should not be studied. Although no patients were excluded from entering the study for this reason, one male patient was subsequently found to have undiagnosed primary hypothyroidism and two male survivors had undiagnosed primary gonadal disease.

Procedure after patients were admitted with a head injury

I performed a full examination of all patients shortly after they were admitted and a record was taken of the therapy given and the results of investigations

that were available. If the patient had none of the exclusion criteria they were considered for recruitment into the study. At this stage informed consent was sought by myself from the patients' relatives. Endocrine tests were then performed using the releasing factor combination. Tests were carried out within 24 hours of the head injury when possible but as some patients were initially admitted to other hospitals in the region before referral to Addenbrookes their first endocrine tests were performed after a greater delay. All endocrine tests were performed by myself.

In-patient course

During their admission neurological status was determined by nursing staff using the Glasgow Coma Scale (Teasdale and Jennett, 1974). The best value obtained within 24 hours of admission was used during subsequent analysis (Jennett, 1979). In addition the duration of post-traumatic amnesia was recorded. In most cases this was determined by myself, but when patients still in PTA were transferred to another region it was determined from their case notes.

The neurological status was the main factor used by the neurosurgeons and neuroanaesthetists to determine whether patients required to be paralysed and ventilated. Those on assisted ventilation for greater than 1 week and those unable to maintain a sufficient oral intake after coming off the ventilator were commenced on parenteral nutrition, supervised by the

nutrition team. It was the neurosurgeon's policy to restrict fluid input to 1 L/24 hours, to attempt to reduce cerebral oedema. This occasionally led to mild hypernatraemia and elevation of the serum urea. If urine output was inappropriately increased urine and plasma osmolalities were measured in order to detect diabetes insipidus.

ROUTINE IN-PATIENT INVESTIGATIONS (performed by neurosurgeons)

Blood Tests

Electrolytes and urea were measured daily until satisfactory oral intake was re-established. A full blood count was taken and repeated later in those patients with multiple injuries who required a blood transfusion. Arterial blood gases were measured several times daily in ventilated patients, who usually had an arterial line in situ.

X Ray Investigations

All patients in the study had a skull X ray performed (AP and lateral). A computerised tomogram brain scan (CT scan) was performed at least once in 40 patients. X rays of other injuries (including facial, pelvic, rib, long bone and vertebral fractures) were performed as necessary.

Other Investigations

Intracranial pressure and central venous pressure were not routinely monitored. Infection screens were carried out where appropriate.

IN-PATIENT THERAPY (Table 5)

Induction of anaesthesia

If artificial ventilation was required thiopentone or midazolam were used to induce anaesthesia. In addition those patients requiring surgery received halothane or nitrous oxide.

Paralysing agents

Pancuronium and alcuronium were used in Addenbrookes. Suxamethonium and d-tubocurarine were occasionally used by the referring hospital.

Analgesia/Sedation

While being artificially ventilated opiate agents were routinely prescribed. The opiate most frequently prescribed was phenoperidine, with fentanyl, morphine and omnopon used less often. During recovery, or if the injury was less severe, aspirin, paracetamol and codeine phosphate were used.

Antibiotics

Ampicillin, flucloxacillin and metronidazole were prescribed in the presence of a skull fracture. Other antibiotics were used infrequently.

Anti-epileptics

Patients with focal or generalised seizures were treated with phenytoin.

Mannitol

29 of the 60 patients required mannitol at some stage after injury to reduce cerebral oedema.

Table 5

DRUGS ADMINISTERED DURING IN-PATIENT ADMISSION

			Number of Subjects
A	During ventilatory support		
	Induction agents	Thiopentone	17
		Midazolam	6
	Neuromuscular blocking agents		
		Pancuronium/ alcuronium	40
		Suxamethonium	18
		d-Tubocurarine	2
	Analgesics/Sedatives		
		Phenoperidine	35
		Fentanyl	13
		Morphine	1
		Omnopon	1
	General Anaesthetic		
		Nitrous oxide	24
		Halothane	24
B	Antibiotics		50
C	Analgesics - non-ventilated subjects	Codeine	15
	- following ventilation	Codeine	22
		Paracetamol	13
		Aspirin	26
D	Anti-epileptic	Phenytoin	15
E	Sedative	Benzodiazepine	8
		Phenothiazine	19
F	H_2 receptor antagonist	Ranitidine	22
G	To reduce cerebral oedema	Mannitol	29
		Dexamethasone	2
H	For diabetes insipidus	DDAVP (desmopressin)	4

Blood transfusion

15 patients received a transfusion because of blood loss due to long bone/pelvic fractures.

Ranitidine

This was prescribed in 22 patients as prophylaxis against stress induced gastric erosions.

PATIENT DETAILS

Age and Sex

There were 36 male survivors, 12 female survivors and 12 fatalities (1 female), producing a male to female ratio of 3:1 in the survivors and 11:1 in the fatalities. The sex distribution of our study group reflects the greater number of head injuries that occur in males. The age distribution of each group is shown in Table 6. The male survivors had 2 peak age ranges for head injuries, between 20-29 years and 40-49 years. The female survivors had 1 peak between 20-29 years and the fatalities had an even distribution between the various age groups. The first peak in the male survivors was largely due to road traffic accidents, whereas the later peak was due to road traffic accidents and falls. The mean age in the male survivors was 36.1 ± 2.7 years (37.8 in those admitted within 24 hours of injury and 34.5 in those studied after 1-3 days - no significant difference). The female survivors had a mean age of 30.0 ± 3.5 years and the fatalities

Table 6 AGE OF SUBJECTS (YEARS)

	Male Survivors	Female Survivors	Fatalities	Total
16-19	5	2	3	10
20-29	11	6	2	19
30-39	3	1	2	6
40-49	10	2	3	15
50-59	4	1	0	5
>60	3	0	2	5

36.2 ± 5.4 years. There was no significant age difference between any of the groups.

Cause of Injury

The cause of the injury is demonstrated in Table 7. Traffic accidents were responsible for 49 of the 60 injuries. In the 47 male subjects car accidents were the most frequent cause of head injury (13 cases), although motorcycle accidents were also common (12 cases). As there are far fewer motorcycles than cars this confirms that motorcyclists have a much greater risk of accident and injury. There were no motorcycle injuries in the females. Despite the large proportion of bicycles in Cambridge (and East Anglia) only 5 of the 60 subjects had been injured when cycling. A greater proportion of the fatalities were cyclists or pedestrians when compared to the survivors (50 % v 25 %). This may reflect the lack of protection from injury in pedestrians and cyclists.

Delay in performing test

The shortest delay between injury and the first releasing factor test occurred in the group of male survivors examined within 24 hours of injury, although it was not significantly shorter than the delay in the group of fatalities ($p < 0.06$) (Table 8). The longest delays occurred in the second group of males and the

Table 7 CAUSE OF INJURY

	Survivors		Fatalities	Total
	Male	Female		
Car accident	11	7	2	20
Motorcycle accident	9	0	3	12
Bicycle hit by vehicle	3	0	2	5
Pedestrian knocked down by vehicle	5	3	4	12
Fall	6	2	0	8
Work Injury	1	0	0	1
Shotgun Injury	0	0	1	1
Assault	1	0	0	1

Table 8 DELAY IN HOURS BETWEEN INJURY AND FIRST RELEASING FACTOR TEST

Fatalities	Female Survivors	Male Survivors	
21.8 ± 4.9	47.1 ± 8.9	Group 1 n=17	14.5 ± 1.3
		Group 2 n=19	41.6 ± 3.8

female subjects, both of which were significantly longer than the other 2 groups ($p < 0.01$).

Severity of Injury

The severity of the brain injury was determined by the best value for the Glasgow Coma Scale within 24 hours of injury. A score of less than 8 indicates that the patient is still in a coma (Jennett, 1979). From Table 9A it can be seen that none of the fatalities came out of a coma during the first 24 hours after injury, whereas 27 of the 48 survivors did. The mean value in the male survivors was 9.5 ± 0.6 (9.9 ± 0.8 in those studied within 24 hours and 9.1 ± 0.8 in those studied after 1-3 days). There was a similar mean value in the females (9.0 ± 0.9), which was not significantly different from the males. The fatalities had a significantly lower value than both the male and female surviors (4.0 ± 0.5, $p < 0.001$).

The second index of the severity of injury was the duration of post-traumatic amnesia. A major head injury is defined by PTA of greater than 24 hours duration (Russell and Smith, 1961). As 40 of the 48 survivors had PTA lasting more than 1 week many of the patients studied had sustained very severe head injuries (Table 9B).

Table 9A GLASGOW COMA SCALE (BEST VALUE WITHIN 24 HOURS)

	Male Survivors (n=36)	Female Survivors (n=12)	Fatalities (n=12)
3-5	6	2	10
6-8	9	4	2
9-12	13	3	0
13-15	8	3	0

Table 9B DURATION OF PTA

	Male Survivors n=36	Female Survivors n=12
24hrs - 1 week	5	3
1 week - 1 month	13	3
1 month - 3 months	11	5
>3 months	7	1

Assisted ventilation

Assisted ventilation was required in 24 of the 36 males, 6 of the 12 females and all of the fatalities. During their ventilatory support and subsequent management many drugs were administered and they are shown in Table 5.

Fractures

Skull fractures occurred in 32 of the 60 subjects (Table 10). Multiple fractures (involving more than 2 bones) and fractures of the parietal bone were the most common fractures (9 cases each). Temporal fractures were also common, whereas frontal, occipital and basal fractures were less frequent. Fracture lines were thought to involve the pituitary fossa in 5 subjects. Only 3 of the 12 fatalities had no fracture compared to 25 of the 48 survivors, reflecting the greater severity of the injury in the fatalities.

Fractures in other bones were common, occurring in 24 of the 48 survivors and 9 of the 12 fatalities. The most frequently fractured bones were the long bones, closely followed by the ribs (including the clavicles) and the facial bones (Table 11). Other injuries were uncommon with 1 patient requiring repair of an aortic tear and another requiring an operation for a compound eye injury. During the first week after injury 24 operations were performed (Table 12). Evacuation of an extradural or subdural haematoma was the most frequent

Table 10 FREQUENCY AND SITE OF SKULL FRACTURES

	Survivors		Fatalities	Total
	Male	Female		
Frontal	1	2	0	3
Fronto-Parietal	0	0	1	1
Parietal	4	0	1	5
Temporal	0	3	2	5
Tempero-Parietal	2	1	0	3
Basal (Pit Fossa)	2(1)	0	1	3(1)
Multiple (Pit Fossa)	4(1)	1	4(3)	9(4)
Occipital	3	0	0	3
No Boney Injury	20	5	3	28
Total	36	12	12	60

Table 11 FRACTURES OTHER THAN SKULL FRACTURES

	Survivors		Fatalities	Total
	Male	Female		
Long Bone	8	1	4	13
Wrist/Ankle/ Patella	3	3	1	7
Ribs/Clavicle	6	2	3	11
Facial	4	4	2	10
Vertebral	2	0	2	4

Table 12 OPERATIONS PERFORMED DURING FIRST WEEK AFTER INJURY

	Survivors		Fatalities
	Male	Female	
Evacuation of:			
subdural haematoma	1	2	1
extradural haematoma	2	3(1)	0
Elevation of depressed skull fracture	1	1	0
Orthopaedic operation	4(2)	3(3)	1(1)
Eye operation	1	0	0
Aortic Repair	1(1)	0	0
Facial operation	0	3(3)	0
Total	10	12	2

Operations performed between the first and second releasing factor test are in brackets.

operation (9 operations), with orthopaedic operations required in 8 cases. Thirteen of the operations were performed before the first releasing factor test, with 11 operations occurring betwen the first and second test.

Neurological complications

Neurological complications were frequent (Table 13). Hemiparesis and cranial nerve palsies were the most common, both occurring in 9 survivors. Post-traumatic seizures developed in 7 subjects. Impairment of intellectual function was reported to some extent by every survivor. All noticed a deterioration in concentration and short-term memory.

METHODS

COMBINED RELEASING FACTOR TEST

As soon as possible after admission to the Neurotrauma Unit patients received intravenous infusions of 4 hypothalamic releasing hormones; human corticotropin-releasing hormone (hCRH 100 ug), human growth hormone-releasing hormone (hGRH 100 ug), thyrotropin releasing hormone (TRH 200 ug) and gonadotropin releasing hormone (GnRH 100 ug). The combination was administered through an intravenous cannula in the antecubital fossa, as sequential 30 sec

Table 13 NEUROLOGICAL COMPLICATIONS

	Male Survivors	Female Survivors
Paraparesis	1	0
Hemiparesis	5	4
Quadriparesis	4	1
Cranial Nerve Palsy		
CN1	0	1
CN3	2	1
CN6	1	1
CN7	3	0
Seizures	5	2

boluses in the order listed. Blood samples for hormone assay were taken at 0, 30, 60 and 120 min from the opposite arm through another indwelling intravenous cannula, which was flushed with heparinised saline to keep the line open.

The releasing factor combination was administered within 24 hours of admission, or as soon as possible thereafter if the patient had been transferred from another hospital. During the infusion and blood testing patients had continuous blood pressure and electrocardiographic monitoring. The protocol was approved by the Addenbrooke's Hospital Ethical Committee.

Follow-up tests

All surviving patients had a repeat releasing factor test performed 7 days after the initial test (7-10 days after injury). A further review and releasing factor test was performed 3-6 months after injury in those patients residing or still hospitalised in East Anglia. Patients (and where appropriate close relatives or medical staff) were questioned about the development of endocrine symptoms since the injury (including diabetes insipidus). The patients therapy was noted and a full examination performed with all neurological and endocrine abnormalities recorded. Any patients found to have a reduced cortisol response during the releasing factor test had an insulin stress test performed.

Releasing factors

Synthetic hCRH and hGRH (1-29 amide), purchased from Bachem UK Ltd, were dissolved in acidified saline (0.02% HCl in 0.9% saline), as previously described (Grossman et al, 1982). GnRH (Ayerst Laboratories) and TRH (Roche Pharmaceuticals) were purchased and prepared according to the manufacturers' instructions.

HORMONE ASSAYS

All assays were performed by laboratory staff of the Department of Biochemistry, Addenbrooke's Hospital except for free testosterone assays which were carried out by myself. The interassay coefficients of variation for each method are included in brackets.

T4 Double antibody radioimunnoassay using ANS to displace T4 from TBG (in house method, cv 4.4% at 96 nmol/L).

T3 Double antibody PEG assisted radioimmunoassay (in house method, cv 6.3% at 3.2 nmol/L).

Total Testosterone Solvent extraction followed by 125 I-labelled radioimmunoassay (in house method, cv 8.6% at 17.1 nmol/L).

Free Testosterone DPC Free Testosterone Kit (solid-phase 125 I-labelled radioimmunoassay, cv 8.0% at 70 pmol/L).

Oestradiol Steranti Oestradiol Kit (125 I-labelled radioimmunoassay, cv 8.2% at 497 pmol/L).

GH Double antibody radioimmunoassay using national reagents from Edinburgh SAS laboratory. Standard: 1st IRP 66/217. (cv 7.4% at 4.7 mU/L).

Cortisol 125 I-labelled radioimmunoassay using Amersham 'Amerlex' reagents. (cv 6.4% at 478 nmol/L).

FSH Double antibody radioimmunoassay using national reagents from Chelsea Hospital for Women. Standard: NIBSC 69/104. (cv 7.6% at 4.9 IU/L).

LH Double antibody radioimmunoassay using national reagents from Chelsea Hospital for Women. Standard: NIBSC 68/40. (cv 7.9% at 4.4 IU/L).

Prolactin Double antibody radioimmunoassay using a secondary standard calibrated against NIBSC 75/504. (cv 9.0% at 493 mU/L).

TSH In the initial half of the study this was determined using an immunoradiometric assay using monoclonal antibodies and a 'sandwich' technique. Standard: 2nd IRP 80/558. In the latter half it was determined by a sensitive enzyme amplified immunoassay, using alkaline phosphatase as the label (IQ Bio Ltd, Cambridge, cv 7.4% at 8.5 mU/L).

All assays participate in the National Quality Control Schemes.

HISTOPATHOLOGICAL STUDY

Twelve of the patients (11 male and 1 female) subsequently died and their clinical details are presented in Table 14. In 8 cases both the hypothalamus

Table 14 CLINICAL DETAILS OF FATALITIES

Age	Sex	Time of Test (hrs after injury)	Survival	GCS	Skull Fracture	DI
32	M	13	1 day	3	Multiple	No
41	M	2	4 hours	3	Multiple (fossa)	No
27	M	10	5 days	5	Occipital	No
20	M	14	8 days	4	No	Yes
46	M	36	9 days	6	Multiple (Basal)	Yes
19	M	23	4 days	3	No	Yes
64	M	23	2 days	3	Multiple (fossa)	No
73	M	23	3 days	3	Parietal	No
17	M	23	3 days	8	Basal	No
16	M	19	2 days	3	No	Yes
29	M	22	2 days	3	Parietal	No
43	F	25	3 days	3	Multiple	Yes

and pituitary were available for study. In a further 2 cases the pituitary only was available and in another 2 cases the hypothalamus only was available.

The aims of this study were to determine the site, extent and frequency of damage to the hypothalamus and pituitary and to compare these findings with the premortem endocrine function tests. It was also hoped that prognostic indicators might be determined.

Single blocks of the pituitary and hypothalamus were taken and, after paraffin wax embedding, step sections were cut (0.25 mm intervals) to include the principal nuclear masses and tracts. Staining was performed with haemotoxylin and eosin. Line diagrams were drawn of 2 representative pituitary sections from each patient and the mean percentage cross-sectional area of infarction was calculated for each patient using the Reichert-Jung MOP-3 system. Anterior pituitary infarction was defined as large if greater than 75% of the cross-sectional area was necrotic, medium-sized between 25-75% and small if less than 25%.

Immunocytochemical staining was then performed using antisera to ACTH, FSH, LH, TSH, GH and PRL and the extent of staining for each hormone was determined.

STATISTICAL ANALYSIS

The data was transformed logarithmically to produce a normal distribution and the mean values reported are the back-transformations (antilog) of the mean of the log values.

Repeated measures analysis of variance, using a computer program (BMDP Statistical Software, Los Angeles), was performed on the transformed data from the releasing factor tests on admission, 1 week later and after 3-6 months. The admission test results were also subdivided into those obtained from patients within 24 hours of injury and those after 1-3 days. Although changes are reported as significant if $p < 0.05$, as multiple comparisons are made only relationships where $p < 0.01$ should be accepted with confidence.

Spearmans rank correlation coefficients were calculated for the duration of PTA and various endocrine parameters and for the best value for the Glasgow Coma Scale within 24 hours of injury and the same endocrine parameters.

The number of subjects analysed during the first test was 60 (12 females, 12 fatalities and 36 males, 17 of the males being seen within 24 hours). The second test, one week later, was performed on 48 subjects (36 males, and 12 females) and the convalescent test was performed on 10 females and 23 males.

C H A P T E R 3

RESULTS

Cortisol

Growth Hormone

Prolactin

Thyroidal Axis

Gonadal Axis

Basal Hormone Concentration and Size of Increment

Injury Severity and Hormone Concentration

Histological Findings

Endocrine-Histological Comparisons

Diabetes Insipidus

CORTISOL

Male Survivors (Tables 15A and B)

Basal Values

The mean basal value was elevated outside the normal range on admission and was significantly greater than the values after 7-10 days and 3-6 months (both $p < 0.001$). There was no significant difference between the mean values of those patients whose admission test was performed within 24 hours of injury and those in whom the initial test was performed 1-3 days after injury. By 7-10 days although the mean value had fallen into the normal range it remained significantly greater than the 3-6 month value ($p < 0.001$), which was in the middle of the normal range.

Response to CRH

There was an increment in response to CRH during each of the 3 tests, ranging from a mean of 172 nmol/L on admission to 242 nmol/L after 7-10 days. Although the smallest increment occurred on admission it produced the highest peak level because of the elevated basal level. There was no difference between the peak values obtained within 24 hours or 1-3 days. Occasionally the basal cortisol level was so high within 24 hours and 1-3 days of injury that a further increase was not observed.

Table 15

MEAN BASAL CORTISOL LEVELS (nmol/L) + RESPONSE TO CRH

A Male Survivors (mean - SEM, mean + SEM)

	Basal	30'	60'	120'
Admission	807	976	979	904
n = 36	(760,856)	(920,1035)	(922,1038)	(852,959)
Day 7-10	594	836	712	556
n = 36	(560,629)	(788,886)	(627,754)	(525,590)
3-6 months	370	583	569	407
n = 23	(344,398)	(542,627)	(529,612)	(379,438)

B Male Survivors - Admission Test Subdivided

	Basal	30'	60'	120'
Within	813	994	947	889
24 hours	(731,904)	(894,1106)	(852,1054)	(799,989)
n = 17				
After	801	959	1007	907
1-3 days	(725,885)	(868,1060)	(911,1113)	(821,1002)
n = 19				

On admission the values 30 and 60 min after stimulation were similar and this pattern recurred during the subsequent 2 tests, with the 60 min level greater on admission but the 30 min level greater after 7-10 days and 3-6 months. The peak values were higher the shorter the time that had elapsed since injury, such that the 30 and 60 min values on admission were significantly greater than the 30 and 60 min values after 7-10 days ($p < 0.05$ and $p < 0.001$ respectively) and after 3-6 months (both $p < 0.001$). Similarly the 30 and 60 min values after 7-10 days were significantly greater than those after 3-6 months ($p < 0.001$ and $p < 0.01$ respectively).

"Subnormal" Basal Levels and Responses to CRH

Within 3 days of injury all but 4 patients had cortisol levels greater than 500 nmol/L. One patient studied within 24 hours and three studied within 1-3 days had values of 140, 230, 320 and 430 nmol/L respectively. Three of these cases had a peak cortisol value of greater than 700 nmol/L in response to CRH, indicating normal function of the pituitary-adrenal axis. The remaining case (with a basal value of 230 nmol/L) had no response. During subsequent follow-up all 4 patients had normal basal levels, with a normal response to stimulation with CRH. It was considered probable that the subject with no cortisol reponse to CRH had received dexamethasone in the referring

hospital, although there was no record of its administration.

Two patients who initially had levels of greater than 1000 nmol/L were found to have considerably lower levels on retesting 7-10 days later (220 + 390 nmol/L). However their response to CRH was intact (both had a peak cortisol greater than 800 nmol/L) and subsequent tests remained normal. At this timepoint all but one patient with basal levels less than 500 nmol/L had an increment of at least 150 nmol/L. This patient had a normal test at 3-6 months.

Convalescent basal levels 3-6 months later were less than 250 nmol/L in four patients. Three of these patients had peak levels greater than 700 nmol/L, while the remaining patient's cortisol level only rose from 170 to 330 nmol/L. This patient subsequently had an insulin stress test performed which demonstrated an adequate cortisol response to hypoglycaemia.

Female Survivors (Table 15C)

Basal values

The highest mean value occurred on admission but although it was above the upper limit of the normal range it was not significantly greater than the value 1 week later. The 3-6 month value was back in the middle of the normal range and was significantly less than the admission and 7-10 day values ($p < 0.005$ and $p < 0.025$ respectively). The three basal values were similar to

the equivalent basal values in the male survivors, with no significant difference observed.

Response to CRH

As noted in the male survivors there was an increment in response to CRH in each of the 3 tests. However the largest increment occurred on admission (256 nmol/L) and the smallest after 7-10 days (76 nmol/L). During the admission test the 30 and 60 min values were identical, whereas in the subsequent two tests the peak level occurred solely after 30 mins. The 30 and 60 min values on admission were significantly greater than the 30 and 60 min values after 7-10 days ($p < 0.05$ and $p < 0.005$ respectively) and 3-6 months ($p < 0.01$ and $p < 0.005$ respectively). In contrast to the male survivors there was no difference between the response to CRH after 7-10 days and 3-6 months. Although the values achieved after CRH in the female group at 7-10 days were less than those in the male group, only the 60 min value was significantly lower ($p < 0.05$). There was no difference between the male and female groups on admission or after 3-6 months.

"Subnormal" Basal Levels and Responses to CRH

Within three days of injury 3 patients were found to have levels less than 500 nmol/L but each had a good response to CRH (peak greater than 700 nmol/L). One of these patients was noted to have a small increment when

retested after 1 week, which had persisted after 3-6 months. However an insulin stress test demonstrated a normal cortisol response.

Fatalities (Table 15D)

There were 12 patients who died shortly after injury, 11 men and 1 woman. Two of the men survived for more than one week and therefore had a second releasing factor test performed.

The basal value lay between the values in the male and female survivors and was not significantly different from either value. However, in contrast to both groups of survivors, there was no increment in response to CRH stimulation, with the values after CRH actually less than the basal value, although not significantly.

There was a large variation in the basal cortisol levels, with six patients having levels greater than 1000 nmol/L on admission, whereas four patients had levels of 400 nmol/L or less. Three of the patients with low levels (399, 90 + 250 nmol/L) had no increment in response to CRH and were considered to be glucocorticoid deficient. The remaining patient had a subnormal response (400 to 480 nmol/L) and may have had partial glucocorticoid deficiency. Most of the patients with levels greater than 1000 nmol/L had no increment after stimulation and it was considered likely that their cortisol production rate was already maximally stimulated.

Table 15 (cont)

MEAN BASAL CORTISOL LEVELS (nmol/L) + RESPONSE TO CRH

C Female Survivors

	Basal	30'	60'	120'
Admission	728	984	984	804
n = 12	(642,825)	(868,1115)	(868,1115)	709,911)
Day 7-10	635	711	587	499
n = 12	(554,724)	(620,817)	(512,674)	(435,573)
3-6 months	406	624	579	424
n = 10	(354,466)	(544,716)	(505,664)	(369,486)

D Fatalities (n = 12)

Basal	30'	60'	120'
735	659	595	631
(619,873)	(555,782)	(501,707)	(531,749)

Both patients who had two tests performed initially had levels greater than 1000 nmol/L. One was subsequently treated with high dosages of dexamethasone for 3 days and when retested after 7 days his cortisol was still suppressed (70 nmol/L), with no response to stimulation (this subject was the only one in the study to have definitely received steroids and his results are included as his first test was performed prior to steroid administration). The second patient's level had fallen to 370 nmol/L with a good response to stimulation (peak of 750 nmol/L).

Age and Cortisol Level

No relationship was found between the age of the patient and the basal cortisol level on admission or 1 week later.

Summary

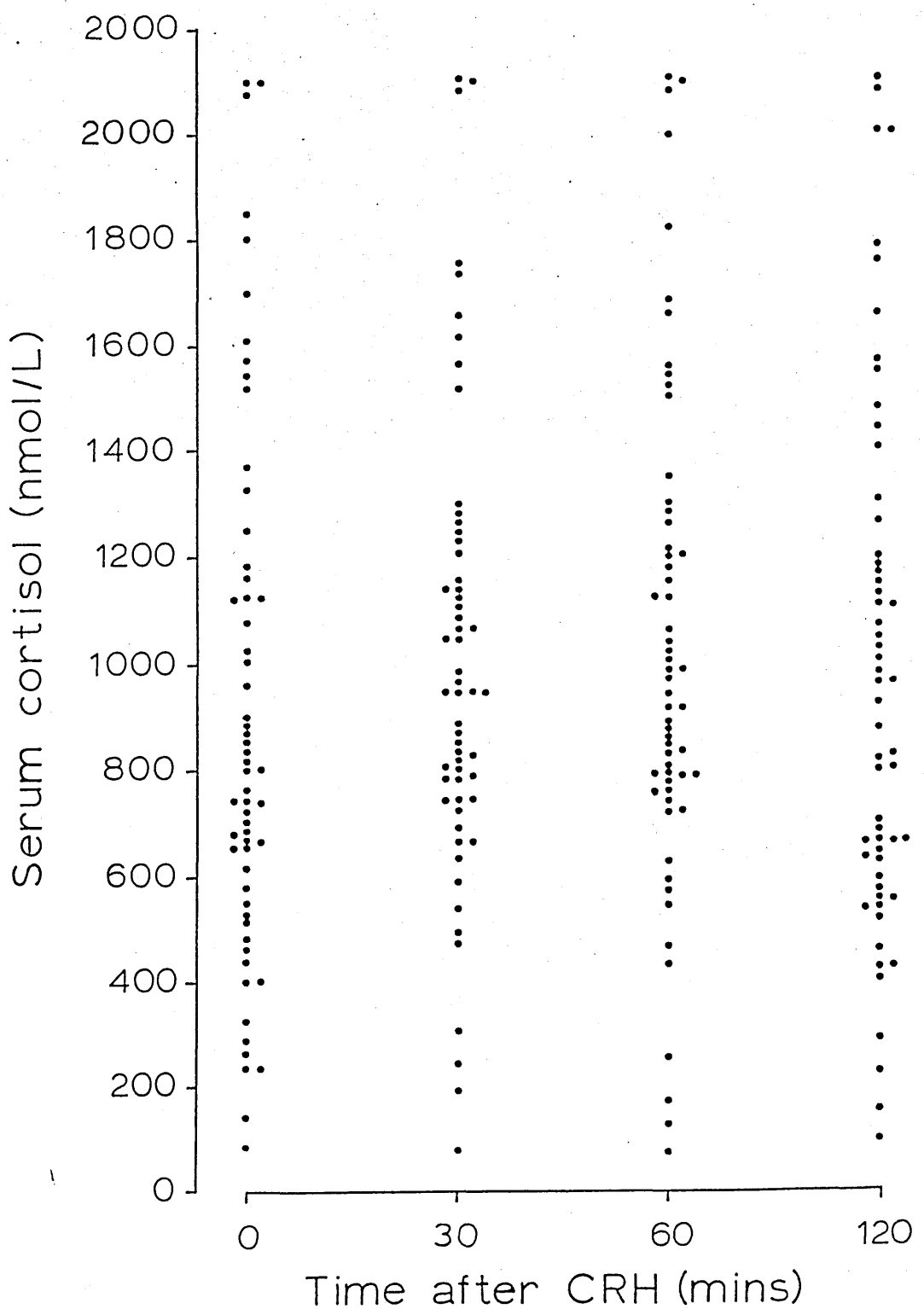
The mean basal cortisol concentrations obtained within the first 3 days after head injury were elevated in the male and female survivors and the fatalities.The highest level occurred in the male survivors but it was not significantly greater than the levels in the other two groups. On retesting the survivors after 7-10 days and 3-6 months there was a stepwise fall of the basal cortisol level into the normal range.

Following stimulation with CRH there was an increment in the cortisol concentration in the

Figure 7

SERUM CORTISOL RESPONSE TO CRH

(Test 1, all 60 subjects)



survivors during each of the 3 tests but not in the fatalities (Fig 7). As for the basal values, there was a stepwise decline from the peak values on admission to the peak values obtained after 3-6 months.

It was assumed that a poor response to CRH was only clinically relevant if the basal cortisol value was less than 500 nmol/L, as significant dysfunction of the pituitary is unlikely with a basal level of this magnitude. A poor response to CRH in patients with a basal level lower than 500 nmol/L was arbitrarily defined as an increment of less than 150 nmol/L, as this cut off point gave a clear division between the various response patterns. Glucocorticoid deficiency was present in 5 of the fatalities, who had low basal cortisol levels and a subnormal or absent response to stimulation with CRH. Two survivors (1 male and 1 female) with basal levels less than 500 nmol/L had subnormal increments when retested after 3-6 months, but their cortisol responses during an insulin stress test were normal.

GROWTH HORMONE

Male Survivors (Tables 16A and B)

Basal Values

The mean basal value was highest on admission and fell gradually to the 3-6 month value. The admission value was significantly greater than both the 7-10 day and 3-6 month values ($p < 0.05$ and $p < 0.005$ respectively). Subdividing the admission values demonstrated a higher value within 24 hours of injury but it was not significantly greater than the 1-3 day value. The mean basal value was within the normal range (<10 mU/L) during all the tests.

Response to GRH

There was an increment in response to GRH during each of the 3 tests. The peak level occurred after 30 mins during each of the tests and it was lowest on admission and highest after 3-6 months. The admission peak value was significantly less than the 7-10 day and 3-6 month values (both $p < 0.001$). There was no significant difference between the 7-10 day and 3-6 month values. Subdividing the admission test results demonstrated no difference in the peak values obtained within 24 hours and after 1-3 days, which were both substantially less than the subsequent results.

Table 16

MEAN BASAL GH LEVELS (mU/L) AND RESPONSE TO GRH

A Male Survivors (Mean - SEM, Mean + SEM)

	Basal	30'	60'	120'
Admission	3.6	6.7	4.9	3.3
n = 33	(3.1,4.2)	(5.7,7.9)	(4.2,5.7)	(2.8,3.8)
Day 7-10	2.4	21.6	10.8	3.7
n = 33	(2.1,2.8)	(18.5,25.1)	(9.3,12.6)	(3.2,4.3)
3-6 months	1.7	28.1	15.1	4.4
n = 21	(1.4,2.1)	(23.0,34.3)	(12.4,18.5)	(3.6,5.4)

B Male Survivors - Admission Test Subdivided

	Basal	30'	60'	120'
Within	4.7	8.1	5.4	3.8
24hrs	(3.7,5.9)	(6.5,10.2)	(4.3,6.8)	(3.1,4.8)
n = 15				
After	2.8	5.7	4.6	2.9
1-3days	(2.3,3.5)	(4.6,7.0)	(3.7,5.6)	(2.3,3.6)
n = 18				

Individual Basal Levels and Responses to GRH

A basal level greater than the upper limit of normal (10 mU/L) occurred in 5 of 33 patients on admission, 2 of 33 subjects one week later and in 1 of 21 subjects after 3-6 months. Predictably, levels less than the lower limit of the assay (1 mU/L) were more frequent the longer the time since injury. On admission 3 of 33 subjects had such levels (all after 1-3 days), one week later 3 of 33 subjects and after 3-6 months 6 of 21 subjects.

On admission the mean peak value was significantly reduced and in 20 of the 30 tests performed at this stage the peak level was less than 10 mU/L. In contrast the 11 tests in which the peak level was greater than 50 mU/L tended to occur at a longer time after injury, with 5 after 1 week and 6 after 3-6 months. Even allowing for this general trend (ie the greater the length of time since injury the higher the peak level), there was substantial variability between individuals as demonstrated by the wide range of peak values on admission (1.2-37 mU/L) and after 3-6 months (4.9-150 mU/L). Furthermore in 4 of the 10 patients whose highest peak level occurred 1 week after injury the value was more than 30 mU/L greater than the peak after 3-6 months, suggesting that in addition there is considerable intra-patient variability, which cannot be explained by a longer time elapsing since injury.

A basal level less than 1 mU/L was associated with a poor response to GRH during the first week after

injury, with 4 of the 6 cases having peak values less than 5 mU/L, whereas after 3-6 months no such association was present, with 3 of the 6 cases having very high peak levels.

Female Survivors (Table 16C)

Basal Values

As for the male survivors there was a stepwise fall from the admission level to the value after 3-6 months, although it did not achieve significance. The mean values were within the normal range and were similar to the equivalent values in the male survivors.

Response to GRH

The pattern was again similar to the male survivors, with the lowest peak occurring on admission and the highest after 3-6 months, but as above the differences did not achieve significance. The initial reduction in the response to GRH was not as substantial as in the male survivors, such that the peak level on admission in the female group was significantly greater than the male group ($p < 0.005$). The subsequent 2 peak levels were similar in both sexes.

Individual Basal Levels and Responses to GRH

The basal level was elevated on 4 occasions (twice on admission). A level less than 1 mU/L occurred during

9 of the 34 tests, with half the patients having such levels after 3-6 months.

In contrast to the male subjects peak levels less than 10 mU/L were evenly distributed between the 3 tests, whereas the highest peak levels (> 50 mU/L) did tend to occur after 3-6 months (7 of 10 subjects). As noted in the male subjects there was a large variability in the response to GRH with a very wide range of peak values on admission and after 3-6 months (6.8-140 mU/L and 2.4-120 mU/L respectively).

Fatalities (Table 16D)

The mean basal value was similar to the values in the 2 groups of survivors. Four of the 12 subjects had levels less than 1 mU/L on admission and 1 of the 2 patients retested after 1 week had developed a value of < 1 mU/L. Two subjects had levels greater than 10 mU/L, with the highest basal level in the study occurring in the female fatality (25 mU/L).

The peak level was similar to the male survivors peak on admission but was significantly less than the female survivors ($p < 0.01$). Basal levels less than 1 mU/L were associated with a poor response to stimulation, with all 5 cases having peak levels less than 3 mU/L, including 3 who had no increment. The fatality who had developed a low basal level when retested had no response to stimulation with GRH, whereas the other fatality who was retested initially had a basal level less than 1 mU/l with a poor response

Table 16 (cont)

MEAN BASAL GH LEVELS (mU/L) AND RESPONSE TO GRH

C Female Survivors

	Basal	30'	60'	120'
Admission	3.6	18.4	15.9	3.9
n = 12	(2.6,4.9)	(13.6,24.9)	(11.7,21.5)	(2.9,5.3)
Day 7-10	2.8	22.3	12.7	4.3
n = 12	(2.1,3.9)	(16.3,30.6)	(9.3,17.5)	(3.2,6.0)
3-6 month	2.2	25.8	18.7	7.9
n = 10	(1.6,3.0)	(18.5,36.0)	(13.5,26.1)	(5.7,11.1)

D Fatalities (n = 12)

Basal	30'	60'	120'
3.9	7.0	6.3	4.6
(3.0,5.2)	(5.3,9.2)	(4.8,8.3)	(3.5,6.1)

which had increased to a basal level of 5 mU/L with a peak of 90 mU/l on retesting.

Summary

The mean basal GH level was highest on admission and fell gradually to the 3-6 month value. The mean level was within the normal range during each of the 3 tests and was similar in the 3 groups of subjects.

The response to GRH was lowest on admission, although in the female subjects this did not achieve significance. The admission response in the male survivors was similar to the fatalities and both were significantly less than the admission response in the females. There was a large variability in the response to GRH between individuals and there also appeared to be a large intra-subject variability between tests, after allowing for the time elapsed since injury.

PROLACTIN

Male Survivors (Tables 17A and B)

Basal Values

The mean basal values were elevated during all 3 tests. The values on admission and after 7-10 days were similar and both were significantly greater than the 3-6 month value ($p < 0.01$ and $p < 0.005$ respectively). Although the 3-6 month value (191 mU/L) was greater than the current upper limit of our hospital reference range (150 mU/L) it has been suggested that a higher upper limit (200 mU/L) is required, which would place the 3-6 month value within the normal range. The higher admission test occurred within 24 hours of injury, although it was not significantly greater than the 1-3 day value.

Response to TRH

In all 3 tests there was an increment in response to stimulation with TRH, with the peak level occurring after 30 mins. There was no significant difference between the response to TRH on admission and the response during the subsequent two tests, although the lowest values occurred on admission. Similarly, there was no significant difference between the responses when the admission test was subdivided, although the levels within 24 hours of injury were lower. However

Table 17

MEAN BASAL PROLACTIN LEVELS (mU/L) AND RESPONSE TO TRH

A Male Survivors (Mean - SEM, Mean + SEM)

	Basal	30'	60'	120'
Admission	279	1019	615	380
n = 33	(253,307)	(924,1123)	(558,678)	(345,419)
Day 7-10	305	1219	740	444
n = 33	(276,336)	(1106,1344)	(672,816)	(403,490)
3-6 month	191	1232	702	349
n = 21	(170,215)	(1095,1385)	(624,790)	(310,392)

B Male Survivors - Admission Test Subdivided

	Basal	30'	60'	120'
Within	309	864	527	331
24hrs	(266,354)	(744,1003)	(454,612)	(285,384)
n = 15				
After	257	1158	693	424
1-3 days	(225,293)	(1015,1322)	(608,791)	(372,484)
n = 18				

the peak level within 24 hours was significantly less than the 7-10 day and 3-6 month peaks (both $p < 0.025$).

Individual Prolactin Levels and the Response to TRH

Only one patient had a basal level more than 1000 mU/L. This occurred after 7-10 days and was probably related to a short course of treatment with metoclopramide, which was commenced after his first test. When reviewed after 3-6 months his basal value was less than 300 mU/L. Two patients had levels between 600-800 mU/L on admission and one week later but were then transferred elsewhere so that no convalescent samples were available. Two further patients had levels greater than 600 mU/L on isolated occasions after 7-10 days. By 3-6 months only one patient of the 21 tested had a value greater than 400 mU/L (410 mu/L) and he was asymptomatic.

One patient had a level less than the lower limit of the assay (100 mU/L) within 24 hours of injury, whereas this occurred in 4 of 21 patients tested after 3-6 months.

No patients were found to have a subnormal prolactin response to stimulation (peak less than 400 mU/L). Three patients had peak levels between 400-500 mU/L during their first test and one of these patients continued to have peaks of a similar magnitude during subsequent tests. His basal levels were all less than the lower limit of the assay (100 mU/L). The results of his other stimulation tests were normal.

An exaggerated response to stimulation (peak greater than 2000 mU/L) did not occur in any subjects within 24 hours of injury. Within 1-3 days 4 patients had an exaggerated response which had persisted in 2 patients and developed in a further 3 patients 1 week later. Only 1 patient continued to have an exaggerated response after 3-6 months. An elevated basal level was associated with 4 of the 10 exaggerated responses.

Female Survivors (Table 17C)

Basal Values

The mean basal level was highest on admission and remained above the upper limit of normal after 1 week. By 3-6 months the level was back within the normal range and was significantly less than the admission value ($p < 0.025$). The basal levels on admission and after 3-6 months were significantly greater than the corresponding basal values in the male group (both $p < 0.005$), but the value obtained 1 week after admission was not significantly different.

Response to TRH

As noted in the male subjects the peak level occurred after 30 mins in each group and it was lowest during the admission test, although this did not reach significance. The female group had a greater response to TRH than the male group during each of the 3 tests,

with peak, 60 and 120 min results all significantly higher ($p < 0.001$, all results).

Individual Prolactin Levels and the Response to TRH

All but 2 patients had basal prolactin levels outside the normal range on admission (greater than 300 mU/L) and during the first week after injury 9 of the 12 patients had values greater than 700 mU/L. By 3-6 months only 1 patient continued to have a basal value greater than 400 mU/L. One further patient had been commenced on a phenothiazine and had a grossly elevated level (7700 mU/L). No patients had levels less than the lower limit of the assay on admission or after 3-6 months.

No patients had a subnormal prolactin response to stimulation (peak less than 800 mU/L), although 1 patient had a peak of 840 mU/L one week after injury. Her basal level was normal and subsequently during the 3-6 month test her peak level became exaggerated.

An exaggerated prolactin response to stimulation occurred in 9 of the 12 patients (peak greater than 3000 mU/L) at some stage after injury. Apart from the 1 patient who had received psychotropic medication the elevated peak values were between 3000-4500 mU/L. An elevated peak value was noted 4 times on admission, 6 times one week later and 4 times after 3-6 months. On all but one occasion it was associated with an elevated basal value.

Menstrual Disturbances

Three females were amenorrhoeic when reviewed after 3-6 months and a further 3 subjects had a temporary menstrual upset, missing at least 1 cycle after injury. One of the amenorrhoeic subjects was taking phenothiazine medication and had a grossly elevated PRL level (7600 mU/L). The remaining 2 amenorrhoeic subjects had virtually normal basal and peak levels after 3-6 months but 1 week after injury their basal and peak levels had been substantially elevated (both basal levels 1500 mU/L, peak levels > 4000 mU/L). Two of the 3 subjects with a transient menstrual disturbance also had elevated basal and peak values after 1 week (basal values 1000 and 800 mU/L), with normal values by 3-6 months.

Fatalities (Table 17D)

The mean basal prolactin was similar to that observed in the male survivors and was above the upper limit of normal. It was significantly less than the female group's basal value ($p < 0.005$). Although the peak level occurred after 30 min the response was poor, with a mean increment of only 146 mU/L, compared to 740 mU/L in the males and 1869 mU/L in the females. Consequently it was significantly less than the male and females peak value on admission (both $p < 0.001$).

Table 17 (cont)

MEAN BASAL PROLACTIN LEVELS (mU/L) AND RESPONSE TO TRH

C Female Survivors

	Basal	30'	60'	120'
Admission	510	2379	1661	918
n = 12	(430,606)	(2003,2825)	(1398,1972)	(773,1091)
Day 7-10	395	2545	1435	768
n = 12	(330,473)	(2127,3047)	(1199,1718)	(642,920)
3-6 month	20	2478	1468	817
n = 10	(230,342)	(2032,3023)	(1204,1791)	(670,996)

D Fatalities (n = 12)

Basal	30'	60'	120'
236	382	317	257
(193,289)	(311,468)	(259,389)	(210,315)

Three patients had basal levels less than the lower limit of the assay (100 mU/L) and two patients had considerably elevated values (800 + 970 mU/L).

Five patients had either no response or a subnormal response to stimulation, including the three patients with basal levels less than 100 mU/L. No fatalities had an exaggerated response to stimulation.

Both patients who had two tests performed initially had elevated basal values (420 + 340 mU/L) with normal responses to stimulation. On repeat testing they both had no response to stimulation with one having a basal level less than 100 mU/L.

Summary

The mean basal prolactin level was elevated on admission in all 3 groups of subjects and remained elevated in both groups of survivors 1 week later. By 3-6 months the mean value was back within the normal range. During all tests the female survivors had a significantly greater basal and peak level than the male survivors and the fatalities.

The peak response occurred after 30 mins in all groups, although the increment was much reduced in the fatalities. The peak value was also significantly reduced in the male survivors within 24 hours of injury, although none were found to have a subnormal response (peak level less than 400 mU/L). In contrast a subnormal or absent response to stimulation was

observed in 5 of the 12 fatalities. An exaggerated response to stimulation was a relatively frequent finding in the female survivors, occurring in half of them one week after injury and still present in 4 after 3-6 months and it was frequently associated with an elevated basal value. No exaggerated responses occurred in the fatalities and it was uncommon in the male survivors.

Menstrual disorders were common in the female survivors, with 3 reporting amenorrhoea and a further 3 noting at least 1 missed period after injury. Five of these subjects had substantially elevated basal and peak levels 1 week after injury, but only 1 subject (who was taking phenothiazine medication) continued to have a significant elevation after 3-6 months.

Relationship between Cortisol, GH and PRL levels

Within 24 hours of injury the basal GH and PRL levels were significantly correlated ($r=0.399$, $p < 0.02$), but neither were correlated to cortisol. After 1-3 days cortisol levels were lower in more severely injured subjects (see Injury Severity section) and there was a significant negative relationship between the cortisol level and both GH ($r=-0.565$, $p < 0.02$) and PRL ($r=-0.493$, $p < 0.02$). By 7-10 days a positive correlation had become established between cortisol and GH ($r=0.350$, $p < 0.025$) but not with PRL. No correlations were present after 3-6 months.

THYROIDAL AXIS

TSH

The normal range for TSH in the radioimmunoassay used in the study was < 1 mU/L to 4 mU/L. Values reported as less than 1 mU/L were substituted by 1 mU/L during statistical analysis. During the last 6 months of the study a more sensitive enzyme amplified immunoradiometric assay (EAIA) became available with a lower detection limit of 0.04 mU/L, which enabled values of < 1 mU/L to be used in the statistical analysis.

Male Survivors (Tables 18A and B)

Basal Values

There was a stepwise increase in mean basal values, with the lowest value occurring on admission and the highest value after 3-6 months ($p < 0.005$). There was no difference between the values obtained within 24 hours and 1-3 days.

One patient was found to have a basal level of 24 mU/L within 24 hours of injury with a peak response of 124 mU/L. Primary hypothyroidism was diagnosed (thyroid antibodies positive) and he was commenced on thyroxine therapy.

Table 18

MEAN BASAL TSH LEVELS (mU/L) AND RESPONSE TO TRH

A Male Survivors (Mean - SEM, Mean + SEM)

	Basal	30'	60'	120'
Admission	1.0	13.7	9.3	4.8
n = 33	(0.9,1.1)	(12.5,15.1)	(8.5,10.2)	(4.4,5.3)
Day 7-10	1.2	11.3	7.7	4.2
n = 33	(1.1,1.3)	(10.3,12.4)	(7.0,8.4)	(3.8,4.6)
3-6 months	1.5	14.8	10.2	6.2
n = 21	(1.4,1.7)	(13.2,16.6)	(9.1,11.4)	(5.5,6.9)

B Male Survivors - Admission Test Subdivided

	Basal	30'	60'	120'
Within	1.0	14.6	9.6	5.3
24hrs	(0.9,1.2)	(12.6,17.0)	(8.3,11.2)	(4.6,6.2)
n = 15				
After	1.0	13.1	9.0	4.5
1-3 days	(0.9,1.2)	(11.4,14.9)	(7.9,10.3)	(3.9,5.1)
n = 18				

TSH Response to TRH

The mean TSH level rose after stimulation to peak at 30 mins during each of the 3 tests. The highest peak value occurred after 3-6 months, followed by the peak on admission. The 7-10 day peak, 60 and 120 min values were significantly less than the 3-6 month values (all $p < 0.05$). There was no difference between the admission tests within 24 hours and those tested after 1-3 days.

Basal TSH and the Response to TRH

Within 24 hours of injury 13 of 15 patients had levels reported as less than 1 mU/L (the remaining patients had levels of 1.1 + 1.2 mU/l). This high proportion gradually reduced during subsequent tests and within 1-3 days 9 of 18 patients, within 7-10 days 13 of 33 patients and by 3-6 months 4 of 21 patients had levels less than 1 mU/L. No patients had this level during all 3 tests.

Only 4 of these patients with levels less than 1 mU/L had a subnormal TSH response to TRH (peak level < 7 mU/L). Three of them had levels less than 1 mU/L and a subnormal TSH response during both their admission test and 1 week later. The remaining patient developed a transient reduction in his basal level after 1 week, which was associated with a subnormal TSH response. The basal TSH concentration was determined by the more sensitive enzyme amplified immunoradiometric assay

during 5 of these 7 abnormal tests. The basal values were subnormal on 3 occasions (0.1, 0.2 and 0.2 mU/L NR 0.4-4 mU/L) and at the lower end of the normal range in the remaining 2 tests (0.6 and 0.7 mU/L). None of the patients tested after 3-6 months had a subnormal response.

An exaggerated response to stimulation (peak greater than 27 mU/L - excluding the patient with primary hypothyroidism) was observed in 2 patients within 3 days of injury and persisted in 1 patient on retesting 1 week later (peak 30 mU/L). He was not retested at 3-6 months but 2 other patients had developed peaks of 28-30 mU/L at that time. All 4 patients had normal basal TSH levels at the time of their exaggerated response.

Female Survivors (Table 18C)

Basal Values

In contrast to the male survivors the mean basal values were similar in the 3 groups, with no significant difference noted. All means were within the normal range and none were significantly different from the corresponding means in the male survivors.

TSH Response to TRH

The peak level occurred after 30 mins and the highest peak occurred after 3-6 months, although it was similar to the peak value on admission. As noted in the

male survivors the lowest values in response to TRH occurred after 7-10 days, although in the female group this did not achieve significance. During each of the 3 tests the female group had higher values in response to TRH than the male group, but not significantly.

Basal TSH and the Response to TRH

On admission basal levels less than 1 mU/L were less frequent than in the male survivors, only occurring in 4 cases. All 4 patients had a normal TSH response to TRH. One week later 3 of these patients and 2 further patients had levels less than 1 mU/L. At this stage one patient, with a basal level of 0.7 mU/L (determined by EAIA), had a borderline normal TSH response to TRH (peak 7 mU/L). After 3-6 months 3 of these patients continued to have levels less than 1 mU/L but within the normal range (0.9, 0.9 and 0.5 mU/L). The TSH response was just within normal limits in the patient with the basal value of 0.5 mU/L (peak 7.6 mU/L).

An exaggerated response to stimulation occurred in only 1 patient and was present during all of her 3 tests. The peak levels were 43 mU/L on admission, 44 mU/L after 1 week and 59 mU/L after 3-6 months. The basal TSH, total T4 and total T3 were within normal limits during the 3 tests and her thyroid antibodies were negative. The patient was asymtomatic when reviewed at 3-6 months. These findings are consistent

with central hypothyroidism or subclinical primary hypothyroidism.

Fatalities (Table 18D)

The mean basal level was within the normal range and was not significantly different from the 2 groups of survivors. Although the peak level occurred 30 mins after stimulation with TRH the increment was much reduced. All values after stimulation were significantly less than the values in the survivors (peak level: $p < 0.001$ compared to male and female survivors).

Seven of the twelve patients had basal levels less than 1 mU/L. Three of these patients had samples analysed by the enzyme amplified assay which gave values of 0.96, 0.12 and 0.12 mU/L (NR 0.4-4 mU/L).

Four subjects had no response to stimulation with TRH (all had basal levels less than 1 mU/L, including the 2 with values of 0.12 mU/L) and three subjects had subnormal responses (peak less than 7 mU/L). A further patient who initially had a normal response, developed a basal level less than 1 mU/L on retesting, with no response to stimulation and the second patient who was retested had developed a subnormal response. Thus no response or a subnormal response to stimulation with TRH occurred in 9 of the 12 fatalities.

Two of the remaining 3 patients had an exaggerated response to stimulation despite having normal basal values (peaks of 29 and 41 mU/L).

Table 18 (Cont)

MEAN BASAL TSH LEVELS (mU/L) AND RESPONSE TO TRH

C Female Survivors

	Basal	30'	60'	120'
Admission	1.6	18.3	12.7	6.7
n = 12	(1.3,1.8)	(15.5,21.6)	(10.7,14.9)	(5.7,7.9)
Day 7-10	1.5	15.0	9.2	5.5
n = 12	(1.3,1.8)	(12.6,17.8)	(7.8,11.0)	(4.6,6.5)
3-6 month	1.4	18.4	12.6	7.7
n = 10	(1.2,1.7)	(15.4,22.1)	(10.5,15.0)	(6.4,9.2)

D Fatalities (n = 12)

Basal	30'	60'	120'
0.9	3.3	3.1	2.4
(0.6,1.1)	(2.5,4.4)	(2.4,4.1)	(1.8,3.2)

TOTAL THYROXINE (Tables 19 and 21)

This was lowest on admission but remained within the normal range. The fatalities had the lowest mean thyroxine level and it was significantly lower than both the male and female survivors admission values (both $p < 0.025$). In both groups of survivors the admission level was significantly less than the 7-10 day value ($p < 0.025$ and $p < 0.05$ in males and females respectively). Although the 7-10 day value was also greater than the 3-6 month value in both groups this did not achieve significance. The female group had higher levels than the males at each of the 3 tests but again these differences were not significant. There was no difference produced by subdividing the male survivors admission test results.

Subnormal thyroxine levels occurred in 8 survivors within 3 days of injury and remained low in 2 patients when retested a week later. One of these cases (who remains lost to follow up) had a subnormal TSH response to TRH on both occasions. Another patient developed a low level 1 week after injury and this was associated with a subnormal TSH response to stimulation. When retested after 3-6 months his thyroxine and TSH response were normal. None of the 3-6 month thyroxine levels were subnormal.

A subnormal thyroxine occurred in 5 of the fatalities and was associated with a subnormal TSH

response to TRH in 4 cases and a subnormal basal TSH level in 2 cases.

One patient had a transient elevation of his total thyroxine 7 days after injury (163 nmol/L). However his free thyroxine was normal (18 pmol/L) and subsequently his 3-6 month test was also normal.

Total Tri-Iodothyronine (T3) (Tables 20 and 21)

T3 levels reported as less than 0.5 nmol/L (the lower limit of the assay) were substituted by 0.5 nmol/l during statistical analysis.

All 3 groups had mean levels that were less than the lower limit of normal (1 nmol/L) on admission and the male survivors continued to have a subnormal mean level 1 week later. All subsequent mean values were within the normal range. Although the admission T3 was lower in the fatalities than the male and female survivors, it did not reach significance. In the male survivors the highest value occurred after 3-6 months and this was significantly greater than the two previous values (both $p < 0.001$). Similarly in the females the 3-6 month value was significantly greater than the admission value ($p < 0.001$) but it just failed to achieve significance when compared to the 7-10 day value. There was no significant difference between the male and female results during any of the 3 tests.

Examination of individual results revealed that values less than or equal to 1 nmol/L (the lower limit of normal) occurred in 29 of 45 survivors within 3 days

Table 19

THYROXINE LEVELS (nmol/L) (Mean - SEM, Mean + SEM)

n = 33

	Males	Females	Fatalities
Admission	84.5	90.8	70.6
	(80.7,88.4)	(86.3,95.5)	(65.4,76.8)
Day 7-10	96.6	104.2	
	(92.4,101.1)	(99.0,109.6)	
3-6 months	92.5	102.8	
	(87.6,97.7)	(95.3,106.5)	

Table 20

TRI-IODOTHYRONINE LEVELS (nmol/L) (n = 33)

(Mean - SEM, Mean + SEM)

	Males	Females	Fatalities
Admission	0.87	0.79	0.70
	(0.82,0.93)	(0.71,0.88)	(0.61,0.79)
Day 7-10	0.97	1.13	
	(0.91,1.03)	(1.02,1.20)	
3-6 months	1.54	1.48	
	(1.48,1.72)	(1.31,1.66)	

Table 21

ADMISSION T4 and T3 SUBDIVIDED

	Thyroxine	Tri-iodothyronine
Within 24 hrs (n = 15)	85.8 (79.7,92.3)	0.93 (0.83,1.03)
Day 1-3 (n = 18)	83.4 (78.2,89.0)	0.83 (0.75,0.91)

of injury, 20 of 45 survivors after 1 week and none of the 31 survivors tested after 3-6 months. An even greater proportion of the fatalities had subnormal values on admission (9 of 12) and six had values less than the lower limit of the assay (0.5 nmol/L). Four of the 5 fatalities with a low T4 also had a low T3.

The one survivor with a transiently elevated thyroxine level was also the only patient to have an elevated T3 in the study (2.5 nmol/L).

Relationship between basal TSH and T4 and T3

No correlation was present between the basal TSH and T4 until 3-6 months after injury, when a significant positive correlation was present ($r=0.408$, $p < 0.03$). In contrast a significant correlation was present with T3 by 7-10 days ($r=0.329$, $p < 0.04$), which was strengthened after 3-6 months ($r=0.420$, $p < 0.03$).

Relationship between T4 and T3

The T4 and T3 were correlated at all times, with the higher correlation coefficients shortly after injury (admission $r=0.694$; day 7-10 $r=0.539$ both $p < 0.001$) and the lowest after 3-6 months ($r=0.495$, $p < 0.01$).

Summary

On admission there was no difference between the mean basal TSH in the 2 groups of survivors and the fatalities and in subsequent tests the two groups of survivors also had similar results. In male survivors the mean basal TSH concentration was lowest on admission and gradually rose in stepwise fashion to its highest level after 3-6 months, whereas in female survivors the basal level was similar during the 3 tests. A basal TSH less than the lower limit of the assay (1 mU/L) was a frequent finding in male survivors within 24 hours of injury and in fatalities. In both these groups subnormal and low-normal basal TSH concentrations measured by EAIA were associated with an impaired TSH response to TRH.

The peak level in response to stimulation occurred after 30 mins in the survivors and fatalities. In survivors there was a reduction in the TSH response to TRH during the first week after injury, which was significant after 7-10 days in the males. The largest TSH response to stimulation occurred after 3-6 months.

The lowest response to stimulation occurred in the fatalities, 9 of whom had a subnormal or absent response to stimulation. Four survivors had a subnormal TSH response to stimulation within 10 days of injury, although by 3-6 months no patients were found to have this pattern.

Minimal elevations of the TSH response to TRH above the upper limit of normal were observed in 5

patients at various times after injury. Two patients (1 fatality and 1 female survivor) had more substantial peaks (41 and 59 mU/L) with normal basal levels. These findings could be explained by central hypothyroidism or subclinical hypothyroidism.

Thyroxine levels were lowest in the fatalities and were occasionally associated with a subnormal basal TSH level and an impaired TSH response to TRH. In the survivors the lowest values occurred on admission and were significantly lower than the values 1 week later. In both groups of survivors the mean after 1 week was greater than the 3-6 month value (not significantly), suggesting that there was a rebound increase in production of thyroxine after the initial fall.

The T3 levels were also lowest in the fatalities but not significantly. In survivors the 3-6 month value was significantly greater than the admission value. The T4 and T3 were significantly correlated at all times, with the greatest correlation coefficients shortly after injury. There was no significant difference between the T4 levels in the males and females or between the T3 levels. The basal TSH was correlated to the T3 one week after injury and to both the T4 and T3 after 3-6 months.

The patient found to have primary hypothyroidism had a thyroxine of 48 nmol/L, a T3 of 0.6 nmol/L and a basal TSH of 24 mU/L, which rose to 126 mU/l after stimulation with TRH. He was commenced on thyroxine replacement therapy.

GONADAL AXIS

FSH

Male Survivors (Tables 22A and B)

Basal Values

The mean basal values were within normal limits during each of the 3 tests. However as the lower limit of normal is poorly defined and taken as the lower limit of the assay, subnormal levels would not have been detected. The lowest mean level occurred after 7-10 days and it was significantly less than both the admission and 3-6 month values ($p < 0.025$ and $p < 0.005$ respectively). Subdivision of the admission values demonstrated that the reduction in basal FSH occurred within 1-3 days of injury, as there was a significant fall from the value within 24 hours of injury to the value after 1-3 days ($p < 0.025$). The value within 24 hours was similar to the 3-6 month value, whereas the 1-3 day value was similar to the 7-10 day value.

Consequently values reported as less than 1 IU/L (lower limit of the assay) occurred in 4 of 15 patients (27%) within 24 hours, rising to 8 of 18 (44%) after 1-3 days and 15 of 33 (45%) after 7-10 days. By 3 months only 1 of 21 patients (5%) continued to have a level less than 1 IU/L.

Table 22

MEAN BASAL FSH LEVELS (IU/L) AND RESPONSE TO GnRH

A Male Survivors (Mean - SEM, Mean + SEM)

	Basal	30'	60'	120'
Admission	1.7	5.6	6.1	5.3
n = 33	(1.5,1.8)	(5.1,6.1)	(5.5,6.7)	(4.8,5.8)
Day 7-10	1.3	2.9	3.0	2.7
n = 33	(1.2,1.4)	(2.6,3.2)	(2.7,3.3)	(2.4,2.9)
3-6 month	2.0	4.7	4.6	4.3
n = 17	(1.8,2.3)	(4.2,5.3)	(4.0,5.2)	(3.8,4.9)

B Male Survivors - Admission Test Subdivided

	Basal	30'	60'	120'
Within	2.2	6.6	8.0	6.7
24 hrs	(1.9,2.7)	(5.6,7.4)	(6.7,9.5)	(5.6,7.9)
n = 15				
After	1.3	4.8	4.9	4.4
1-3 days	(1.1,1.5)	(4.1,5.7)	(4.2,5.7)	(3.7,5.1)
n = 18				

FSH Response to GnRH

The peak level occurred after 60 mins, apart from the convalescent test at 3-6 months when the 30 min value was just greater than the 60 min value.

The highest peak level occurred on admission and it was significantly greater than the 7-10 day and 3-6 month values ($p < 0.001$ and $p < 0.05$ respectively). In keeping with the fall in basal FSH the increment in response to GnRH was much reduced 7-10 days after injury and at this stage all values after stimulation were significantly less than the values on admission ($p < 0.001$) and after 3-6 months ($p < 0.005$). Subdividing the admission test results demonstrated that the peak value within 24 hours of injury was significantly greater than the value after 1-3 days ($p < 0.025$). However the reason for this difference was not the same as for basal FSH, as the peak level after 1-3 days was not reduced when compared to the 3-6 month value. The significant difference had been produced by a relative increase in the FSH response within 24 hours of injury.

Individual FSH Levels and the Response to GnRH

Two elderly patients had elevated basal FSH and LH values during all 3 tests. They both gave a history of loss of libido and impotence prior to their head injury and therefore it was considered likely that they had primary gonadal failure unrelated to their injury. Their results were excluded from statistical analysis.

One further patient had an elevated value on admission, which had returned to normal one week later. Elevated values did not occur in any other patient.

Within 24 hours of injury a peak value of greater than 10.5 IU/L (the upper limit for the peak in our hospital's reference range) in response to GnRH occurred in 8 of 15 patients (53%) compared to 3 of 18 between day 1-3 (17%), 1 of 33 one week later (3%) and 0 of 17 after 3-6 months (0%). The two patients with presumed primary hypogonadism had exaggerated responses during all tests and were not included in these results.

There was only one patient who had a peak level less than 1.5 IU/L (the lower limit for the peak in our hospital's reference range). His peak level was subnormal on initial testing (day 1-3) and one week later but had returned to normal by 3-6 months. During the 2 tests with reduced peak levels his basal values were less than 1 IU/L, whereas the normal peak after 3-6 months was associated with a higher basal value. By choosing a threshold of 3 IU/L it was possible to demonstrate the much diminished response present after 7-10 days. During this period 19 of 33 (58%) patients had a peak less than 3 IU/L compared to 3 of 15 (20%) within 24 hours, 5 of 17 (28%) within 1-3 days and 2 of 17 (12%) after 3-6 months.

Female Survivors

Basal FSH (Table 22C)

The mean basal levels were within normal limits in all groups. The lowest level occurred after 7-10 days but it was not significantly lower than the admission value. Both were significantly less than the value after 3-6 months (admission: $p < 0.05$ and 7-10 days: $p < 0.025$). The 3-6 month value was also significantly greater than the equivalent value in the male group ($p < 0.05$), whereas there was no sex difference between the previous 2 tests.

FSH Response to GnRH

The peak value occurred after 60 mins in each group. The highest value following stimulation with GnRH was after 3-6 months but it was not significantly greater than the admission or 7-10 day values. The female group had a significantly greater peak level compared to the male group during each of the 3 tests (admission: $p < 0.05$, 7-10 days: $p < 0.001$, 3-6 months: $p < 0.001$).

Individual Basal FSH Levels and the Response to GnRH

Two patients were post-menopausal and their results were excluded from statistical analysis. Both had basal values within the normal range on admission which had become grossly elevated by 3-6 months. Their

FSH response to stimulation had also become exaggerated by 3-6 months. No pre-menopausal patients had basal values greater than the upper limit of normal during any test. A value less than the lower limit of the assay occurred in 2 patients on admission and 3 patients one week later.

Two patients had a subnormal response to stimulation with GnRH (peak less than 3 IU/L), both on admission. Their basal levels were less than the lower limit of the assay during these subnormal responses. Their subsequent tests were within normal limits.

An exaggerated response occurred in 7 of 10 subjects on admission, 4 of 9 subjects one week later and 3 of 8 subjects after 3-6 months. Two of the three patients with a persistently exaggerated response were amenorrhoeic and the third patient had missed 2 periods before her cycle had recommenced.

Fatalities (Table 22D)

Two of the male fatalities had primary gonadal disease and their results were excluded from statistical analysis. Both had grossly elevated basal gonadotrophin levels and an exaggerated response to stimulation. One patient was aged 32 years and had small atrophic testes at postmortem and the other was aged 73 years. The female fatality was also excluded from the analysis.

The mean basal FSH was within normal limits but was significantly greater than both the male and female

Table 22 (cont)

MEAN BASAL FSH LEVELS (IU/L) AND RESPONSE TO GnRH

C Female Survivors

	Basal	30'	60'	120'
Admission	1.6	8.6	8.8	8.0
n = 10	(1.3,2.0)	(7.0,10.6)	(7.2,10.8)	(6.5,9.9)
Day 7-10	1.4	8.5	8.8	7.6
n = 9	(1.2,1.8)	(6.8,10.5)	(7.1,10.9)	(6.1,9.4)
3-6 months	2.8	8.7	9.4	8.4
n = 8	(2.2,3.6)	(6.9,11.0)	(7.5,11.9)	(6.7,10.6)

D Fatalities (n = 9)

Basal	30'	60'	120
4.3	7.7	7.8	7.3
(3.4,5.4)	(6.1,9.8)	(6.2,9.9)	(5.8,9.3)

survivors results ($p < 0.001$ and $p < 0.005$ respectively). No fatalities had a basal level less than the lower limit of the assay and two had an elevated basal level.

The peak level occurred after 60 mins and it was within the normal range. It was intermediate between the male and female survivors but was not significantly different from either group. Four of the nine male fatalities (excluding the 2 with primary gonadal disease) had an exaggerated response and 1 had a subnormal response.

Both fatalities who were retested after 1 week had no change in their basal levels although their peak levels became lower (subnormal in one).

Summary

Altough the mean basal FSH concentrations remained within normal limits in all groups the fatalities had a significantly greater value than the male or female survivors on admission. A fall in FSH levels occurred in the male survivors within 1-3 days of injury and remained low 1 week later. A similar pattern may have been present in the females as their admission values were lower than the 3-6 month values. However not enough females were tested shortly after injury to enable the admission test results to be subdivided. The only difference in basal values between the 2 groups of survivors occurred after 3-6 months when the level was significantly greater in the females than the males.

The peak value after stimulation occurred after 60 mins in the fatalities and survivors. The male survivors had their highest level within 24 hours of injury, followed by a substantial reduction in the peak level achieved after 7-10 days. No such pattern was apparent in the females, who had similar peak levels during each test. Their peak was significantly greater than the male survivors during each test. The peak value in the fatalities was intermediate between both groups of survivors. The 3 survivors (2F, 1M) who had temporary subnormal peak responses had subnormal basal levels during these tests (<1 IU/L). No patients had a subnormal response when retested after 3-6 months. Three female patients who had experienced disruption of their menstrual cycle continued to have an exaggerated FSH response to stimulation with GnRH after 3-6 months.

LH

Male Survivors (Tables 23A and B)

Basal Values

Although there was a stepwise increase in the mean basal value from admission to 3-6 months this did not reach significance. However subdivision of the admission tests demonstrated that the value within 24 hours of injury was similar to the 3-6 month value, whereas the 1-3 day value was lower than all other basal values and was significantly reduced ($p < 0.025$) when compared to the 24 hour value. It was the only mean value less than the lower limit of normal (3 IU/L). This pattern, with a reduction after 1-3 days maintained for 1 week, is identical to that observed for FSH. Consequently the majority of results less than the lower limit for the hospital's reference range (3 IU/L) occurred after 1-3 days (12 of 18, 67%) and 7-10 days (13 of 33, 39%) when compared to within 24 hours (4 of 15, 27%) and after 3-6 months (3 of 21, 14%).

Subnormal basal levels, particularly shortly after injury, were frequently associated with an exaggerated response to stimulation.

LH Response to GnRH

During each of the 3 tests the peak level occurred after 30 mins and was exaggerated (greater than hospital reference range of 27 IU/L) on admission and

Table 23

MEAN BASAL LH LEVELS (IU/L) AND RESPONSE TO GnRH

A Male Survivors (Mean - SEM, Mean + SEM)

	Basal	30'	60'	120'
Admission	3.4	40.5	34.5	26.7
n = 33	(3.1,3.8)	(36.7,44.7)	(31.3,38.0)	(24.3,29.4)
Day 7-10	3.6	27.5	22.0	17.1
n = 33	(3.3,4.0)	(24.9,30.4)	(19.9,24.3)	(15.4,18.8)
3-6 month	4.2	22.6	19.8	15.4
n = 17	(3.7,4.8)	20.0,25.6)	(17.5,22.4)	(13.6,17.4)

B Male Survivors - Admission Test Subdivided

	Basal	30'	60'	120'
Within	4.5	44.7	40.6	30.5
24hrs	(3.8,5.4)	(32.8,53.0)	(34.3,48.1)	(25.7,36.1)
n = 15				
After	2.7	37.3	30.1	23.8
1-3 days	(2.3,3.1)	(32.0,43.6)	(25.8,35.1)	(20.4,27.8)
n = 18				

after 7-10 days. The largest response occurred within 24 hours of injury although it was not significantly greater than the 1-3 day value. On admission all the values after stimulation with GnRH were significantly greater than the 7-10 day values (all $p < 0.005$) and the 3-6 month values (all $p < 0.001$). There was no significant difference between the 7-10 day and 3-6 month values.

Individual Responses to GnRH (Fig. 8)

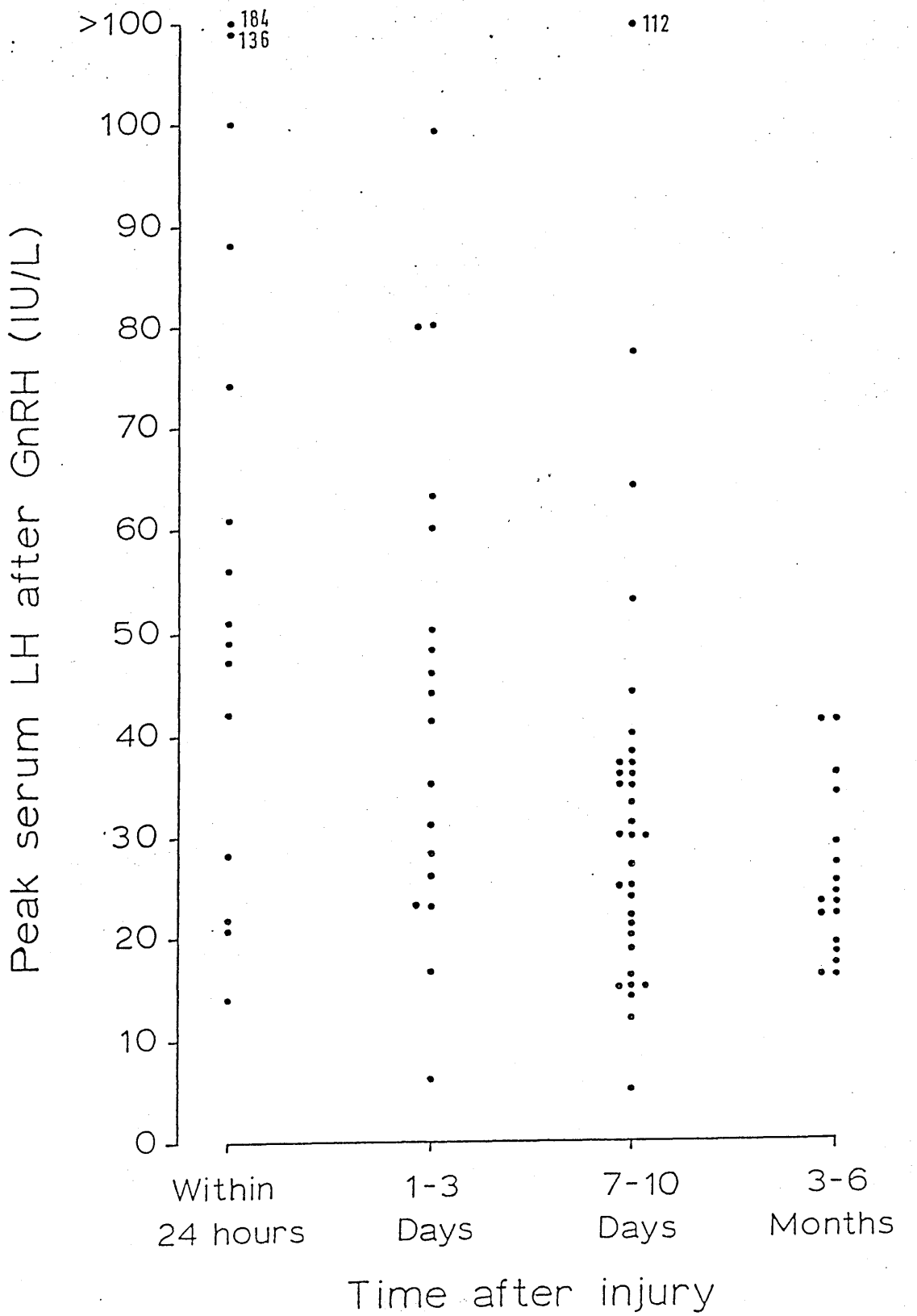
The 2 elderly patients with presumed primary gonadal disease had elevated basal LH levels and an exaggerated response to stimulation during all 3 tests. Their results were not included in the statistical analysis.

Only 1 patient had an elevated basal level (greater than 10 IU/L) and this occurred within 24 hours of injury. His subsequent levels were normal. Three patients with a subnormal basal level after 3-6 months had a normal LH response to stimulation.

A grossly exaggerated response of more than twice the normal peak (greater than 54 IU/L) occurred in 8 of 15 (53%) patients within 24 hours, falling to 6 of 18 (33 %) after 1-3 days, 4 of 33 (12%) after 7-10 days and in no patients after 3-6 months. Three patients had peak levels greater than 100 IU/L within 24 hours of injury, with the highest peak recorded at 185 IU/L. In the group reviewed after 3-6 months 5 of 17 (29%) patients continued to have a peak greater than the

Figure 8

CHANGE IN PEAK SERUM LH AFTER INJURY
(Male survivors)



normal limit (27 IU/L). These 5 patients all had an exaggerated response during their first test and 3 also had an exaggerated response during their second test.

A subnormal response (peak less than 7 IU/L) occurred in 2 patients. This was observed after 1-3 days in one patient and after 7-10 days in the other and was associated with subnormal basal levels. Both patients had a normal response when retested after 3-6 months.

Female Survivors

Basal Values (Tables 23C)

The mean basal values had the same pattern as the male survivors with the lowest level on admission and the highest level after 3-6 months, but as with the males there was no significant difference. However the values on admission and after 7-10 days were less than the lower limit of normal (2.5 IU/L) and were significantly less than the corresponding values in the male survivors (both $p < 0.025$).

LH response to GnRH

The peak value occurred after 30 mins during each test. The highest value after stimulation was on admission and it was significantly greater than the values one week and 3-6 months later (both $p < 0.05$), which were similar. The admission peak level was greater than the upper limit of normal (35 IU/L),

whereas the 7-10 day and 3-6 month levels were within the normal range. There was no significant difference between the male and female responses during any of the 3 tests.

Individual Basal LH Levels and the Response to GnRH

The 2 post-menopausal patients had basal LH values within the normal range during the first week after injury, which became grossly elevated by 3-6 months. Their LH response to stimulation was also greatly increased after 3-6 months. Their results were excluded from this analysis.

After 3-6 months one patient had a basal LH level greater than normal, with an exaggerated LH response, but her menstrual cycle had returned to normal.

Subnormal basal LH values were common, occurring in 9 of the 10 (90%) pre-menopausal patients on admission. Seven (70%) continued to have subnormal levels one week later. Three of the eight pre-menopausal patients retested after 3-6 months had subnormal levels and two of them were amenorrhoeic. Two of the subnormal basal levels were associated with an exaggerated LH response to stimulation (1 of the amenorrhoeic subjects), with the remaining response within normal limits.

Despite the frequent finding of subnormal basal levels only one patient had a subnormal LH response to stimulation. This occurred after one week and was

normal again after 3-6 months. On both occasions the basal level was subnormal.

An exaggerated response to stimulation occurred in 7 of the 10 (70%) pre-menopausal patients on admission and was present in 5 out of 9 (56%) one week later. After 3-6 months 4 out of 8 patients continued to have an exaggerated response, although the maximum value had fallen from 272 IU/L on admission to 48 IU/L. On many occasions an exaggerated response was associated with a subnormal basal level.

Fatalities (Table 23D)

The results from the two fatalities with primary gonadal disease were excluded from this analysis. Both had elevated basal levels and an exaggerated response to stimulation.

The mean basal level was within normal limits, although it was significantly greater than both the male survivors ($p < 0.025$) and female survivors ($p < 0.001$) basal values. Three of the 9 male fatalities, without primary gonadal disease, had an elevated basal level, as did the one female fatality. One fatality had a subnormal basal level, which was associated with a grossly exaggerated response to stimulation (peak 230 IU/L).

The peak level occurred after 30 mins and it was significantly less than the peak admission values in both groups of survivors (both $p < 0.01$). Three patients had no LH response to stimulation, with two

Table 23 (cont)

MEAN BASAL LH LEVELS (IU/L) AND RESPONSE TO GnRH

C Female Survivors

	Basal	30'	60'	120'
Admission	1.9	49.4	44.7	31.1
n = 10	(1.5,2.4)	(38.1,64.1)	(34.5,58.0)	(24.0,40.3)
Day 7-10	2.0	28.0	22.4	15.9
n = 9	(1.6,2.7)	(21.3,29.5)	(17.1,29.5)	(12.1,20.8)
3-6months	3.3	28.6	22.8	17.1
n = 8	(2.5,4.4)	(21.4,38.2)	(17.1,30.5)	(12.8,23.2)

D Fatalities (n = 9)

Basal	30'	60'	120'
6.8	19.5	17.3	12.9
(5.2,8.9)	(15.0,25.3)	(13.3,22.5)	(10.0,16.8)

having normal basal levels and one having an elevated value. Four patients had an exaggerated response (including the female and excluding the subjects with primary gonadal disease). Two of these had an elevated basal level, one had a normal level and one had a subnormal level.

The two fatalities who were retested after 1 week had normal basal levels during both tests. One had a normal response to stimulation during both tests, whereas the other initially had an exaggerated response which had become subnormal on retesting.

Relationship Between Basal FSH and Basal LH

A significant relationship was present at all times after injury, with the strongest correlation present on admission ($r=0.774$, $p < 0.001$) and the weakest after 7-10 days ($r=0.379$, $p < 0.02$).

Summary

The mean basal LH concentration was highest in the fatalities and was significantly greater than both the male and female survivors on admission. The male survivors had a significant fall in level between 24 hours and 1-3 days of injury, with the level becoming subnormal. However, their mean value for the first 3 days after injury was within the normal range and was significantly greater than the value for the female survivors, which was subnormal. One week later the

basal value remained subnormal in the females and was still significantly less than the males. After 3-6 months the value had risen and there was no significant difference between the sexes.

The peak value after stimulation occurred at 30 mins in the fatalities and survivors. Both groups of survivors had exaggerated peak levels on admission, with a stepwise reduction to the 3-6 month values, which were within the normal range. The peak value in the fatalities was significantly less than the values in the 2 groups of survivors. An exaggerated response to stimulation shortly after injury was frequently associated with a subnormal basal LH concentration. However on 3 occasions a subnormal basal level was associated with an impaired response to stimulation.

Four of the 8 pre-menopausal females (one of whom was amenorrhoeic) and 5 of the 21 males who were retested after 3-6 months continued to have an exaggerated response to stimulation. No patients had a subnormal response at this time.

The basal FSH and basal LH were significantly correlated at all times after injury.

MALE SURVIVORS

Total Testosterone (Tables 24 and 26)

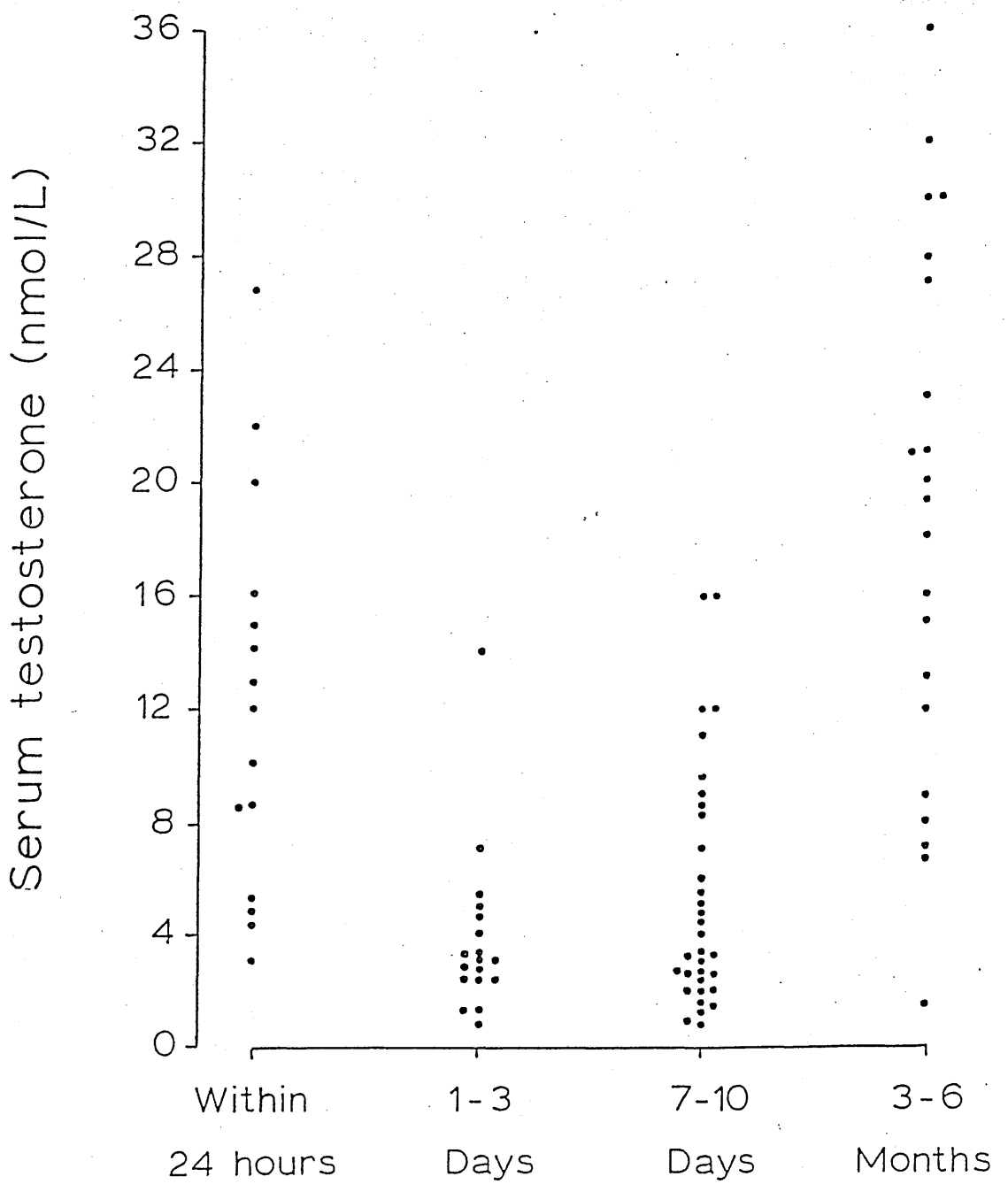
The mean total testosterone was subnormal on admission and had decreased further 1 week later, although not significantly. By 3-6 months the value was back in the middle of the normal range and it was significantly greater than the 2 previous values (both $p < 0.001$). Subdividing the admission test results demonstrated that within 24 hours of injury the testosterone concentration had begun to fall and was already just below the lower limit of normal. The nadir was reached by 1-3 days and this level was significantly less than within 24 hours ($p < 0.001$).

Examination of individual results (Fig 9) revealed that 8 of 15 (53%) patients had a value in the normal range within 24 hours of injury, whereas this had fallen to 1 of 18 (6%) by 1-3 days and 5 of 33 (15%) by 7-10 days. By 3-6 months 16 of 21 (76%) patients had values within the normal range. The 5 patients who continued to have subnormal values after 3-6 months had developed hypogonadal symptoms.

All but two of the thirty-three male survivors (3 were excluded because of primary hypogonadal or thyroidal disease) had a subnormal testosterone level during the first week after injury. The two exceptions had nadirs of 11 and 12 nmol/L.

Figure 9

CHANGE IN SERUM TESTOSTERONE AFTER INJURY
(Male survivors only)



Relationship Between Testosterone and Basal and Stimulated Gonadotrophin Levels

During the course of the study a testosterone level was measured on 87 occasions in the 33 male survivors. One third of these levels (29) were within the normal range and only four of these were associated with a subnormal basal LH level and one with a basal FSH less than 1 IU/L. The remaining two thirds (58) of testosterone levels were subnormal and could be divided into one half (29) with normal basal LH levels and one half (29) with subnormal basal LH levels. An FSH level less than 1 IU/L (the lower limit of normal) occurred in 26 of the 58 cases with a subnormal testosterone and in 18 of the 29 cases with a subnormal LH and testosterone. Thus a normal testosterone level was rarely associated with a subnormal basal gonadotrophin level, whereas a subnormal testosterone level was associated with a subnormal basal LH in half the cases and a basal FSH less than 1 IU/L in just under half the cases.

An exaggerated peak FSH level occurred 12 times and was associated with a normal testosterone on 6 occasions and a subnormal testosterone in the remaining 6 cases. On each occasion an exaggerated peak LH response was also present.

An exaggerated peak LH level occurred 47 times and was present on 14 of the 29 occasions that the testosterone level was normal and on 33 of the 58 occasions when the testosterone was subnormal.

Fatalities

The mean testosterone was significantly greater in the fatalities ($p < 0.001$). Only one fatality had a subnormal level on admission (5.4 nmol/L), although both patients that were retested had developed low levels by the time of the second test (4.4 and 2.4 nmol/L). At the time of the low testosterone levels all three patients had no FSH response to stimulation and two had small LH increments (3.0 rising to 5.2 IU/L and 3.3 rising to 4.5 IU/L).

Patients with Persistent Hypogonadism

There were 5 patients, with no previous history of hypogonadism, who continued to have a subnormal testosterone level after 3-6 months, which was associated with the development of hypogonadal symptoms. None of them had elevated basal LH or FSH levels at any stage. At 3-6 months two had a subnormal basal LH level and three had a normal level. Three continued to have an exaggerated LH response to stimulation.

Relationship Between Basal LH and Testosterone Concentrations

There was a strong correlation between the basal LH level and the testosterone concentration on admission ($r=0.614$, $p < 0.001$). The correlation just

failed to achieve significance 1 week later ($r=0.283$, $p < 0.055$) and was no longer present after 3-6 months.

Free Testosterone (Table 25 and 26)

In 17 patients free testosterone was measured on admission and one week later and in 10 of them it was also measured after 3-6 months. The free testosterone level is age dependent with a normal range of 60-140 pmol/L between 20-30 years and 40-100 pmol/L between 60-70 years.

The mean value on admission was subnormal and it had fallen further 1 week later. Both of these values were significantly less than the 3-6 month value ($p < 0.01$ and $p < 0.001$ respectively), which was back in the normal range. Subdivision of the admission value demonstrated that there was a significant fall from the value within 24 hours, which was probably just subnormal, to the value after 1-3 days which was the lowest value recorded ($p < 0.005$).

Very low levels (less than 20 pmol/L) were not found in any patients within 24 hours of injury, but were present in 3 of 6 patients after 1-3 days, 8 of 17 patients one week later and in 1 of 10 patients after 3-6 months.

Three of the five patients who had low total testosterone values after 3-6 months and hypogonadal symptoms also had free testosterone measured. One result was grossly subnormal (7.5 pmol/L) and the other

two patients had values at or just below the lower limit of normal (50 and 51 pmol/L).

The free and total testosterone values were highly significantly correlated ($r=0.868$, $p < 0.001$).

Female Survivors

Oestradiol (Table 27)

The oestradiol concentration was within normal limits for the follicular phase on admission and after 3-6 months, with the lower value on admission but not significantly. However after one week the level was subnormal and significantly less than the 3-6 month value ($p < 0.05$). The one female fatality had a level at the lower limit of normal.

Female Survivors With Menstrual Irregularities

One female was post-menopausal and one was peri-menopausal with a history of irregular periods prior to injury. Eight of the ten pre-menopausal females were reviewed after 3-6 months. Two reported no menstrual upset, three missed 1-3 periods before their cycle was re-estabished and three remained amenorrhoeic.

The oestradiol level was subnormal in the three patients with amenorrhoea. Their basal and peak FSH levels were normal at 3-6 months, but two continued to have subnormal basal LH levels and one also had an exaggerated LH response to stimulation (the patient with pronounced hyperprolactinaemia).

Table 24 TOTAL TESTOSTERONE LEVELS (nmol/L)

		Males	Fatalities (n=12)
Admission	n=33	5.4 (4.8,6.2)	15.1 (12.1,18.8)
Day 7-10	n=33	4.1 (3.6,4.7)	
3-6 months	n=21	15.8 (13.4,18.5)	

Table 25 FREE TESTOSTERONE LEVELS (pmol/L)

		Males
Admission	n=17	36.1 (31.0,42.1)
Day 7-10	n=17	25.0 (21.4,29.1)
3-6 months	n=10	69.2 (57.6,83.6)

Table 26 ADMISSION TOTAL AND FREE TESTOSTERONE LEVELS SUBDIVIDED

	Total Testosterone	Free Testosterone
Within 24hrs	9.6 (8.3,11.1)	49.6 (43.1,57.1)
n = 15		n = 11
After 1-3 days	3.4 (3.0,3.9)	20.0 (16.6,24.2)
n = 18		n = 6

Table 27 OESTRADIOL LEVELS (pmol/L)

Admission	n=10	109 (92,120)
Day 7-10	n=9	77 (65,91)
3-6 months	n=8	124 (102,149)

Summary

Gonadal steroid concentration fell after injury in both the male and female survivors. The mean oestradiol level was subnormal in the female group tested one week after injury and the testosterone level was subnormal in the male groups tested within 24 hours, after 1-3 days and one week later. The fatalities had a significantly greater testosterone level than the male survivors.

The free and total testosterone concentrations were strongly correlated after injury and the basal LH was significantly correlated to the testosterone concentration on admission.

Subnormal testosterone levels were frequently associated with a subnormal basal LH and a basal FSH less than 1 IU/L, whereas normal testosterone levels were rarely accompanied by low basal gonadotrophin values. The proportion of times an exaggerated peak gonadotrophin concentration occurred was similar whether the testosterone level was normal or subnormal and appeared to be more dependent on time since injury than testosterone level.

Persistent hypogonadism was present in 8 (5 males, 3 females) of the 31 patients retested after 3-6 months. The 3 females were amenorrhoeic and the 5 males reported impotence and loss of libido. All 8 had low gonadal steroid concentrations, 5 had subnormal basal

LH concentrations and 4 had an exaggerated LH response to stimulation.

RELATIONSHIP BETWEEN BASAL HORMONE LEVEL AND THE SIZE OF THE INCREMENT IN RESPONSE TO STIMULATION WITH ITS RELEASING FACTOR

Cortisol

In the male and female survivors combined the basal cortisol levels were negatively correlated to the cortisol increment after CRH on admission, ($r=-0.705$, $p < 0.001$), after 7-10 days ($r=-0.265$, $p < 0.04$) and after 3-6 months ($r=-0.699$, $p < 0.001$).

GH

In male survivors there was a close positive correlation on admission and 1 week later between the basal GH level and the GH increment ($r=0.491$, $p < 0.004$ and $r=0.552$, $p < 0.001$ respectively), which was maintained if the female survivors were also included ($r=0.298$, $p < 0.04$ and $r=0.476$, $p < 0.001$ respectively). No relationship was present after 3-6 months.

PRL

There was no relationship observed on admission or after 1 week in either group of survivors. However by 3-6 months both groups had established a significant positive correlation (males $r=0.481$, $p < 0.02$; females $r=0.714$, $p < 0.025$).

TSH

In male survivors many of the results on admission were less than 1 mU/L and most had not been measured by the EAIA, so no correlation was attempted at this time. However a positive correlation was observed on admission in the female survivors ($r=0.639$, $p < 0.02$). One week later a significant correlation was observed in both groups (males $r=0.334$, $p < 0.03$: females $r=0.779$, $p < 0.005$) and was still present after 3-6 months (males $r=0.422$, $p < 0.03$: females $r=0.800$, $p < 0.005$).

FSH

A highly significant positive correlation was present on admission in both the male and female survivors ($r=0.630$, $p < 0.001$ and $r=0.742$, $p < 0.003$ respectively). After 1 week only the male survivors continued to have a significant correlation ($r=0.396$, $p < 0.02$) and by 3-6 months no relationship was present in either group.

LH

The only significant correlation between these 2 variables occurred on admission in both groups of survivors (males $r=0.299$; females $r=0.510$ both $p < 0.05$). After 1 week and 3-6 months no relationship was present.

Summary

At all stages after injury there was a significant negative relationship between the basal cortisol level and the size of the increment in response to CRH, whereas TSH was positively correlated to its increment at all stages. During the first week after injury GH, FSH and LH were correlated to their increment but no relationship was present after 3-6 months. In contrast PRL was only correlated to its increment after 3-6 months.

THE RELATIONSHIP BETWEEN INJURY SEVERITY AND HORMONE CONCENTRATIONS

Cortisol

The injury severity was compared to the basal and peak cortisol levels in the 3 groups of subjects. The GCS was used to determine injury severity but as high scores indicate mild injuries and low scores severe injuries, it is inversely related to injury severity. As it is the relationship with injury severity that is under study all correlation coefficients calculated using the GCS have had their sign changed in this and subsequent sections.

Initially no correlation appeared to be present on admission in male survivors, but subdividing the admission tests revealed significant relationships. In those admitted within 24 hours of injury there was a positive correlation between injury severity and both the basal and peak cortisol levels ($r=0.578$, $p < 0.01$ and $r=0.544$, $p < 0.02$ respectively). However at 1-3 days a negative correlation was found between the basal cortisol and injury severity ($r=-0.488$, $p < 0.03$). By 7-10 days a positive correlation had been re-established ($r=0.369$, $p < 0.02$). No relationship was observed in the female survivors at any stage, in the fatalities or in the male survivors after 3-6 months.

GH levels

There was a strong correlation in male survivors between injury severity and the basal GH level during the first week after injury. The highest correlation coefficient occurred within 24 hours of injury ($r=0.719$, $p < 0.002$) and the relationship remained strong after 1-3 days ($r=0.548$, $p < 0.02$) and 1 week later ($r=0.504$, $p < 0.002$). There was no correlation observed in the female survivors at any stage or in the fatalities. Combining the 2 groups of survivors resulted in the loss of all significant relationships. The only relationship between the peak GH level and injury severity was observed on admission in the male survivors ($r=0.398$, $p < 0.02$).

PRL levels

In both male and female survivors the basal PRL level was correlated to the injury severity on admission ($r=0.433$, $p < 0.01$ and $r=0.545$, $p < 0.04$ respectively). One week later there was a significant correlation in the male survivors only ($r=0.337$, $p < 0.03$).

The peak PRL value had an even stronger relationship with injury severity in the male survivors (on admission $r=0.472$, $p < 0.003$; after 1 week $r=0.596$, $p < 0.001$), although no correlation was present in the female survivors.

TSH levels

No correlation was present between the injury severity and the basal TSH level in any of the groups of subjects at any time (although for the reasons stated previously no correlation was attempted for the male survivors on admission). However on admission the peak TSH was negatively correlated to injury severity in all subjects combined (male and female survivors and fatalities: $r=-0.357$, $p < 0.004$) and all male subjects combined (survivors and fatalities: $r=-0.318$, $p < 0.02$). No correlation was present in individual groups of subjects.

T4 and T3 concentrations

On admission, in the combined group of survivors and fatalities, a significant negative correlation was present between T4 and injury severity ($r=-0.331$, $p < 0.01$) and T3 and injury severity ($r=-0.334$, $p < 0.01$). This relationship persisted in the survivors 1 week later (T4: $r=-0.337$, $p < 0.02$. T3: $r=-0.242$, $p < 0.05$) but was lost by 3-6 months.

Gonadotrophin levels

The only relationship between FSH and injury severity occurred in the male survivors after 7-10 days, at the time of their FSH nadir. At this stage there was a significant negative correlation between

the injury severity and both the basal and peak FSH levels ($r=-0.343$, $p < 0.03$ and $r=-0.368$, $p < 0.02$ respectively). In female survivors after 3-6 months the basal FSH level just failed to achieve significance ($r=-0.582$).

There was no relationship between the injury severity and basal or peak LH levels in the male survivors at any time or in the fatalities. However in the female survivors after 3-6 months a significant negative correlation was achieved for both the basal and peak LH ($r=-0.640$, $p < 0.05$ and $r=-0.788$, $p < 0.01$ respectively).

Testosterone + Oestradiol Concentrations

On admission there was a significant negative correlation ($r=-0.315$, $p < 0.04$) between injury severity and testosterone in the male survivors. No relationship was present in the fatalities or during later tests in the survivors.

There was no relationship between injury severity and the oestradiol concentration at any time.

Summary

There was a significant positive relationship between injury severity and the basal cortisol level within 24 hours of injury and after 1 week, but a negative correlation was present after 1-3 days.

In addition injury severity was positively correlated to the basal GH, basal PRL, peak GH, peak PRL and peak cortisol levels on admission and the basal and peak PRL levels 1 week later.

A negative correlation was present between injury severity and T3, T4, testosterone and peak TSH levels on admission and with T4, T3, basal and peak FSH levels 1 week later.

No relationship was observed with the LH levels in the male survivors or fatalities, although injury severity was significantly negatively correlated to both the basal and peak LH in female survivors after 3-6 months.

HISTOPATHOLOGICAL STUDY

Large infarcts were present in the anterior pituitary glands of 9 cases (Fig 10), no subjects had a medium-sized infarct and a small infarct was present in 1 case. Thus all 10 anterior pituitary glands available for study had evidence of infarction, (two cases were mislaid). The large infarcts were centrally situated, with a thin layer of cells surviving under the capsule and adjacent to the posterior lobe. Pituitary stalk transection occurred in 1 case and it was associated with a small pituitary infarct. This subject died shortly after injury (5 hours), which may not have allowed time for a more substantial pituitary infarct to have developed.

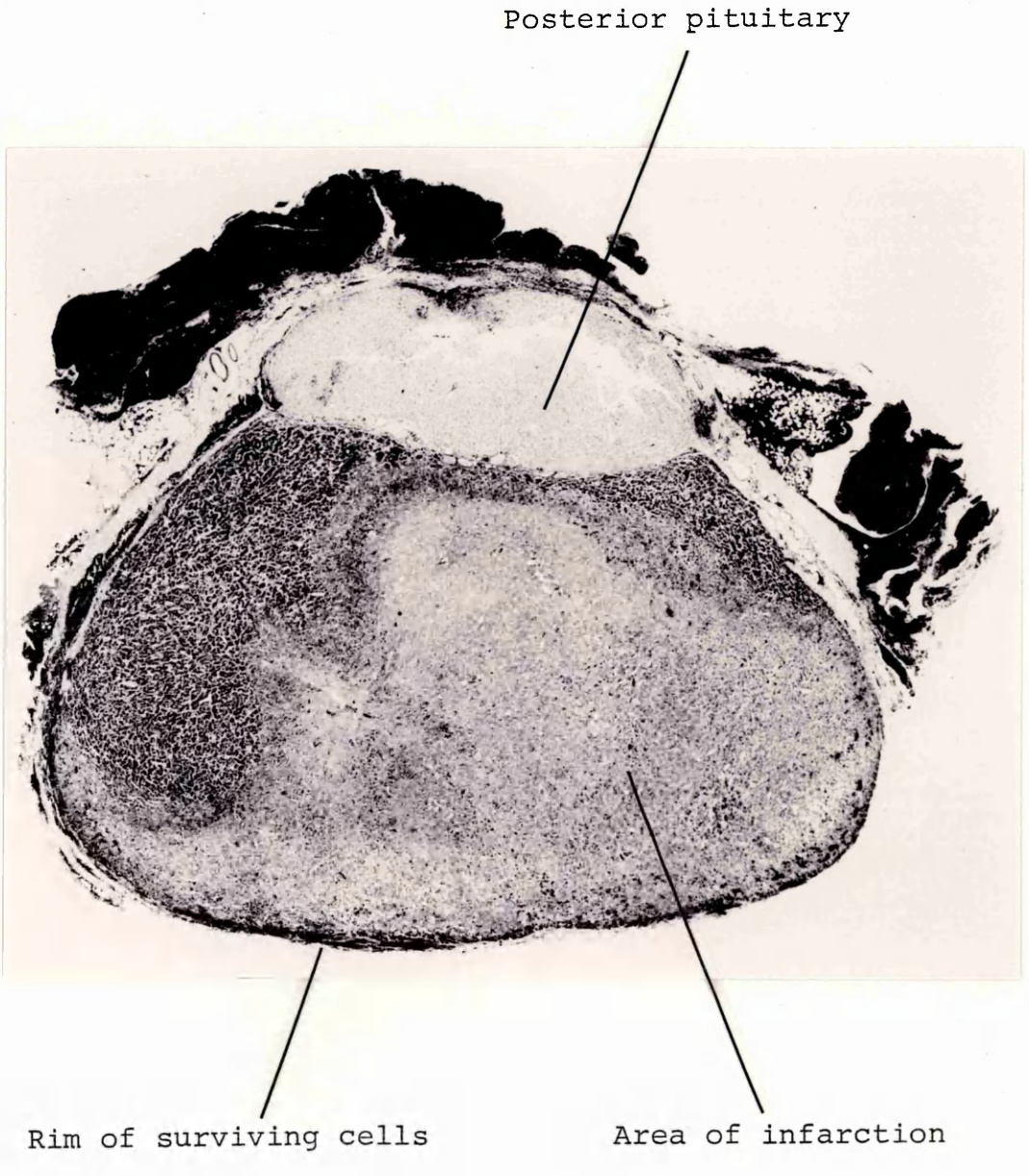
The posterior lobe was normal in 9 of the 10 specimens. In 1 case a small infant was present.

Damage to the hypothalamus was relatively mild, with occasional petechial haemorrhages in the supraoptic or paraventricular nuclei (6 cases), median eminence (3 cases) and the stalk (2 cases). Small areas of infarction were also present in the median eminence in 2 cases.

Skull Fractures and Pituitary Histology

Skull fractures were present in 9 of the fatalities and 6 had multiple fractures involving the base of the skull, 3 of which extended into the pituitary fossa. Five out of these 6 subjects had large

Figure 10 Large anterior pituitary infarct



pituitary infarcts. The one exception had a fracture through the pituitary fossa but only a small pituitary infarct, although the pituitary stalk was transected. Large pituitary infarcts were also observed in the 3 remaining subjects who had single fractures, which involved the occipital bone and the parietal bone (2 subjects). The pituitary gland was available in 1 of the 3 subjects who did not have a skull fracture and it had a large infarct.

Direction of Injuring Force and Pituitary Histology

In 6 cases the impact was predominantly in the antero-posterior plane and in the remaining 6 cases the main impact was from the side. Of the 9 pituitary glands with large infarcts 4 came from subjects who were injured in the antero-posterior direction and 5 came from subjects injured by a lateral force.

Immunocytochemistry

This study was performed on 7 of the 10 anterior pituitary glands from the head-injured fatalities and 3 control glands from subjects who had died from cardiac disease. In glands from the head-injured subjects staining for ACTH, TSH, PRL and FSH tended to be restricted to the periphery of the gland, in areas of surviving tissue. In contrast staining for GH was similar to that in the control subjects, with a positive reaction throughout the gland. Staining for LH

was negative in 6 of the 7 head-injured subjects, but positive in the control subjects.

No relationship was observed between hormone levels and the extent of the staining, although the degree of staining was not assessed quantitatively.

Results of Pituitary Stimulation Tests

The endocrine results from the fatalities have already been presented separately for each axis, but in order to enable comparison with the histology, a further brief summary is included (Table 28). The TSH and PRL responses were frequently deficient, whereas the gonadotrophin responses were usually preserved. Four subjects had an impaired GH response and 5 patients with cortisol levels less than 400 nmol/L and a subnormal response to stimulation with CRH were considered to be glucocorticoid deficient.

Analysing individual patient results demonstrated that 5 subjects had 4 or more deficient hormone responses to stimulation, 4 subjects had 1-3 deficient responses and the remaining 3 subjects had no deficient responses. The 2 patients, who were retested 1 week later, had both undergone marked deterioration in their pituitary response to stimulation.

Endocrine-Histological Comparison

Six of the 9 subjects with large anterior pituitary infarcts had multiple (2 or more) impaired

Table 28

RESPONSE TO RELEASING FACTOR STIMULATION (FATALITIES)

n = 12

	No response	Subnormal response	Total
TSH	6	2	8
PRL	5	1	6
Cort*	4	1	5
GH	3	1	4
FSH	3	0	3
LH	2	1	3

* excluding patients with a basal level greater than 500 nmol/l

hormone responses to stimulation. Two of the remaining 3 cases with large infarcts had normal dynamic tests and 1 had a deficient TSH response only. The subject with the small infarct and pituitary stalk transection had disruption of all axes with no hormone response to stimulation.

One of the 2 subjects in which only the hypothalamus was available had multiple hormone deficiencies and an infarct involving the median eminence. The other subject had normal dynamic endocrine tests and no significant hypothalamic damage.

Multiple deficient hormone responses were present in 5 of the 6 subjects with fractures involving the base of the skull, 2 of the 3 subjects without a skull fracture and in 1 subject with a parietal fracture.

DIABETES INSIPIDUS

This occurred much more frequently in the fatalities than the survivors. Five of the 12 fatalities developed it after injury, whereas it was detected in only 2 of the 48 survivors. The delay before its onset was quite variable in the fatalities, with 2 developing it within 24 hours of injury and the remaining 3 developing it after 3-5 days. In 4 of the fatalities the diagnosis was made from the fluid balance, plasma electrolytes and urine and plasma osmolalities. The DI persisted in all 4 cases and required treatment with DDAVP. The fifth fatality had a transient increase in urine output on day 4-5 associated with an increase in plasma sodium concentration. Although urine and plasma osmolalities were not checked it is likely that this subject had temporary DI, which did not require treatment with DDAVP.

Both survivors that developed DI were female and neither required treatment with DDAVP. In 1 subject it occurred 48 hours after injury and had resolved within a further 24 hours. The second subject was noted to be passing large volumes of dilute urine within 12 hours of injury, which returned to normal during the next 12 hours. Urine and plasma osmolalities were checked in both cases to confirm the diagnosis of DI. When reviewed after 3-6 months neither case had noted a recurrence of their DI.

Endocrine Findings in Subjects with Diabetes Insipidus

In the 2 survivors with transient DI there were no associated anterior pituitary hormone deficiences. As observed in many other survivors who did not develop DI, a subnormal T3, an elevated basal PRL level and an exaggerated LH response to GnRH were present. In contrast deficient anterior pituitary hormone responses to stimulation were present in many of the fatalities with DI, although similar abnormalities were present in fatalities who did not develop DI. Only 1 fatality with DI was found to have normal dynamic testing, although as DI did not occur until 3 days after the test, he might also have developed anterior pituitary deficiences by that stage.

Pathological Findings in Fatalities with Diabetes Insipidus

Vasopressin is synthesised in the supraoptic and paraventricular nuclei of the hypothalamus and is transported down the supraoptic-hypophyseal tract to the posterior pituitary, where it is stored until required. The rapid development of DI in 2 fatalities (within 24 hours of injury) suggests that their pituitary store may have been damaged as well as the hypothalamic sites of synthesis and in 1 of these cases, in which the posterior pituitary was available, areas of infarction were present in the neurohypophsis.

In contrast histological examination of the posterior pituitary was unremarkable in the subjects in whom the onset of DI was delayed for 3-5 days. Hypothalamic histology was similar in all the subjects, with small petechial haemorrhages involving the supraoptic and paraventricular nuclei. In addition 2 subjects had small areas of infarction in the median eminence.

Direction of Injuring Force

Definite evidence of skull impact in the antero-posterior plane was present in 6 of the 7 subjects with DI. In 2 of the fatalities, who did not have a skull fracture, the only evidence of head injury was facial bruising, 3 other subjects had facial fractures and the sixth subject had a large occipital fracture and haematoma. The final subject did not have a skull fracture but the impact appeared to have been from the side, involving the tempero-parietal region. It is interesting to note that 3 of the 5 fatalities with DI did not have a skull fracture.

C H A P T E R 4

PULSATILITY STUDY

Methods of Pulse Analysis

Subjects and Methods

Results

INVESTIGATION OF THE PULSATILE RELEASE OF LH

Our results demonstrate that the typical hormonal pattern in the gonadal axis after head injury is a low gonadal steroid concentration, a subnormal or low-normal basal gonadotrophin concentration and an exaggerated gonadotrophin response to stimulation with GnRH. The combination of a low end-organ hormone concentration with normal basal pituitary trophic hormone levels but an exaggerated pituitary hormone response to stimulation is typical of hypothalamic dysfunction. The hypothalamus is thought to contain the site responsible for GnRH pulse generation, posssibly in the arcuate nucleus (Clarke and Cummins, 1987) and therefore hypothalamic dysfunction can result in abnormal or absent gonadotrophin pulsatility with consequent hypogonadism. In order to further investigate the possibility of hypothalamic dysfunction being responsible for the observed abnormalities in the gonadal axis, the pulsatile release of LH has been studied in a group of head-injured patients.

METHODS OF PULSE ANALYSIS

A review of the endocrine literature reveals that there is no standard method of pulse analysis. Several factors are important in maximising the identification of gonadotrophin pulsations including frequency of blood sampling, method of pulse analysis and assay precision.

The frequency of sampling has been performed every 20 mins in some studies (Santen and Bardin, 1973) and every 2-3 mins in other studies (Veldhuis et al, 1986). Crowley et al (1985) performed 5 min sampling and then analysed his results missing out 3 in every 4 samples (to mimic 20 min sampling), 2 in every 3 samples (15 min sampling) and alternate samples (10 min sampling). He clearly demonstrated that many pulses were missed at sampling intervals of 15 or 20 mins, with little difference between 5 and 10 min intervals. Recently Veldhuis et al (1986) has shown that to capture 90 % of pulses sampling should be every 2-3 mins for 24 hours, although the volume of blood required makes this impractible for many subjects. Clayton (1987) reported that a suitable compromise is a 10 min sampling frequency with as long a duration as possible.

The most commonly used method of pulse analysis is that suggested by Santen and Bardin in 1973, which employs a fixed threshold criterion. A significant peak is present if there is a 20 % or greater increase in hormone concentration above a preceding nadir. As sampling is now performed more frequently it has been suggested that with 5 or 10 min sampling the 20 % increment above the nadir should be present in at least 2 consecutive timepoints (Crowley et al, 1985). It was hoped this method would limit false-positive LH pulses to less than 1 %, but Veldhuis et al (1985) has demonstrated a sixfold increase in the number of false-positive pulses if the intra-assay coefficient of

variation is 8 % compared to 5 %. Thus he has proposed a further refinement of Santen and Bardin's technique by defining the pulse detection threshold in terms of the intra-assay measurement error, which varies with the hormone concentration, enabling the threshold to be adjusted according to the LH concentration. This method reduces both the number of false-positive pulses and the number of true-positive pulses which are overlooked.

A second approach to the problem of pulse identification is to use the sensitive statistical technique of time series analysis (Clark et al, 1987). This consists of spectral analysis, which tests the data for a potentially infinite number of cycles each having a different frequency. In practice the spectrum usually shows either a featureless form indicating no clear periodicity or one or more dominant peaks indicating periodicity with the corresponding frequency. Thus spectral analysis should give some indication of the periodicity of any pulsatility in the data. To safeguard against reporting spurious periodicities and also to give a fitted model for the data it is advisable to perform a periodic regression analysis or harmonic analysis (Clark et al, 1987). This technique assumes a regular periodicity and may be less sensitive if pulses are irregular. However studies using this technique (Murdoch et al, 1985; Bannister et al, 1986; Clark et al, 1987) have reported shorter periodicities than those obtained by using threshold

methods, indicating the increased sensitivity of this technique.

Recently a different approach to pulse identification, developed from the field of chromatography, which may be even more sensitive than time series analysis, has been reported (Oerter et al, 1986). There is an enormous literature on the detection of peaks in chromatography and resolution of overlapping peaks is a frequent problem, but this vast experience in peak detection has not previously been adapted for use in endocrinology. Computer programs for chromatographic peak detection will often work remarkably well when applied to a series of hormone measurements. However their performance can be dramatically improved by incorporating several characteristics of the endocrine data into the program, such as drifting baseline, circadian rhythm, sharp upstroke and trailing exponential downstroke. The program devised by Oerter et al (1986), called "Detect", is based on 2 programs they developed for identification of chromatographic peaks. It contains sections dealing with estimation of measurement error, setting tolerances for derivatives and peak detection, which identifies significant upstrokes and downstrokes taking into account the standard error of observations and of the first and second derivatives. It also has the facility to estimate peak shape, half-life of the peaks decay and the instantaneous secretion rate. This method avoids using artificial or arbitrary criteria,

which are present in all other methods of pulse analysis and every threshold or decision is derived in more than one manner, so that this technique should produce less false positive peaks while being very sensitive.

Assay precision is the final factor which influences pulse identification. As the basic problem of pulse analysis is one of recognising a small signal against a noisy background any factor which reduces this noise (increased assay precision and reduced crossreactivity) will improve pulse detection.

PATIENTS AND METHODS

Informed consent was obtained from relatives before inclusion in the study. The protocol was approved by the Addenbrooke's Hospital Ethical Committee.

Patients

The study was performed on 5 male patients admitted to the Head Injury Unit with a major head injury. Details of the patients age, duration of PTA, Glasgow Coma Scale scores, site of skull fracture, neurological status at the time of the pulsatility study and neurological complications are shown in Table 29.

Four of the 5 patients required assisted ventilation and they received pancuronium and phenoperidine.

Table 29 CLINICAL DETAILS OF HEAD-INJURED PATIENTS

	Day of Test	Age	PTA	GCS	Skull Fracture	Neurological Complication	Neurological Status	Gonadal Dysfunction
JF	6	35	3/52	12	Base	Nil	Artificial Ventilation Not required	Impotence for 2/12
AW	6	25	1/12	15	Parietal	Paraparesis (Spinal injury)	P+V until 48hrs prior to study	Nil
RM	10	49	2/12	11	Parietal	Nil	P+V until 24hrs prior to study	Loss of libido (6/12)
PW	7	43	3/52	10	Parietal	Dysarthia Seizures	P+V until 96hrs prior to study	Loss of libido + impotence (3/12)
GM	9	31	>6/12	4	Base and Facial	PVS	P+V until 72hrs prior to study	Loss of libido (6/12)

Abbreviations PVS - persistent vegetative state

P+V - paralysed and ventilated

In all patients antibiotic cover was provided by flucloxacillin, ampicillin and metronidazole and once patients were breathing spontaneously analgesia was achieved with codeine phosphate. No patients received mannitol or glucocorticoids.

The control group consisted of 6 healthy age-matched males.

Hormone Assays

LH was measured by an immunoradiometric assay (MAIACLONE, Serono Diagnostics, Woking) standardised against WHO 68/40 and with an interbatch coefficient of variation of 5.9% at 7 IU/L and of 5.5% at 46 IU/L. The normal range of this assay for male subjects is 1.8 - 10 IU/L.

Testosterone was measured by ether extraction followed by radioimmunoassay using reagents from St Thomas's Hospital, London.

Experimental Protocol

Samples were taken for testosterone and LH within 24 hours of injury (Day 1) in all but 1 patient who was transferred from another hospital, in whom the first sample was taken 40 hours after injury. Daily samples were then obtained for the next 4 days (Day 2 to Day 5), with further samples between Day 10-14 and after 3-6 months.

Combined releasing factor tests were performed as in the main study (on admission, after 1 week and 3-6 months).

The pulsatility study was performed between Day 6-10, with sampling commencing between 6-7 AM. Blood was taken without stasis via an indwelling venous cannula at intervals of 5 minutes for 4 hours after which sampling was at 15 minute intervals for a further 2 hours.

Pulse analysis was performed using a fixed threshold technique, time series analysis and the "detect" program. For the threshold method an LH pulse was defined as an increment in LH concentration from nadir to peak of greater than 20 % in two or more consecutive samples and the pulse amplitude was calculated as the difference between the peak and the preceding nadir.

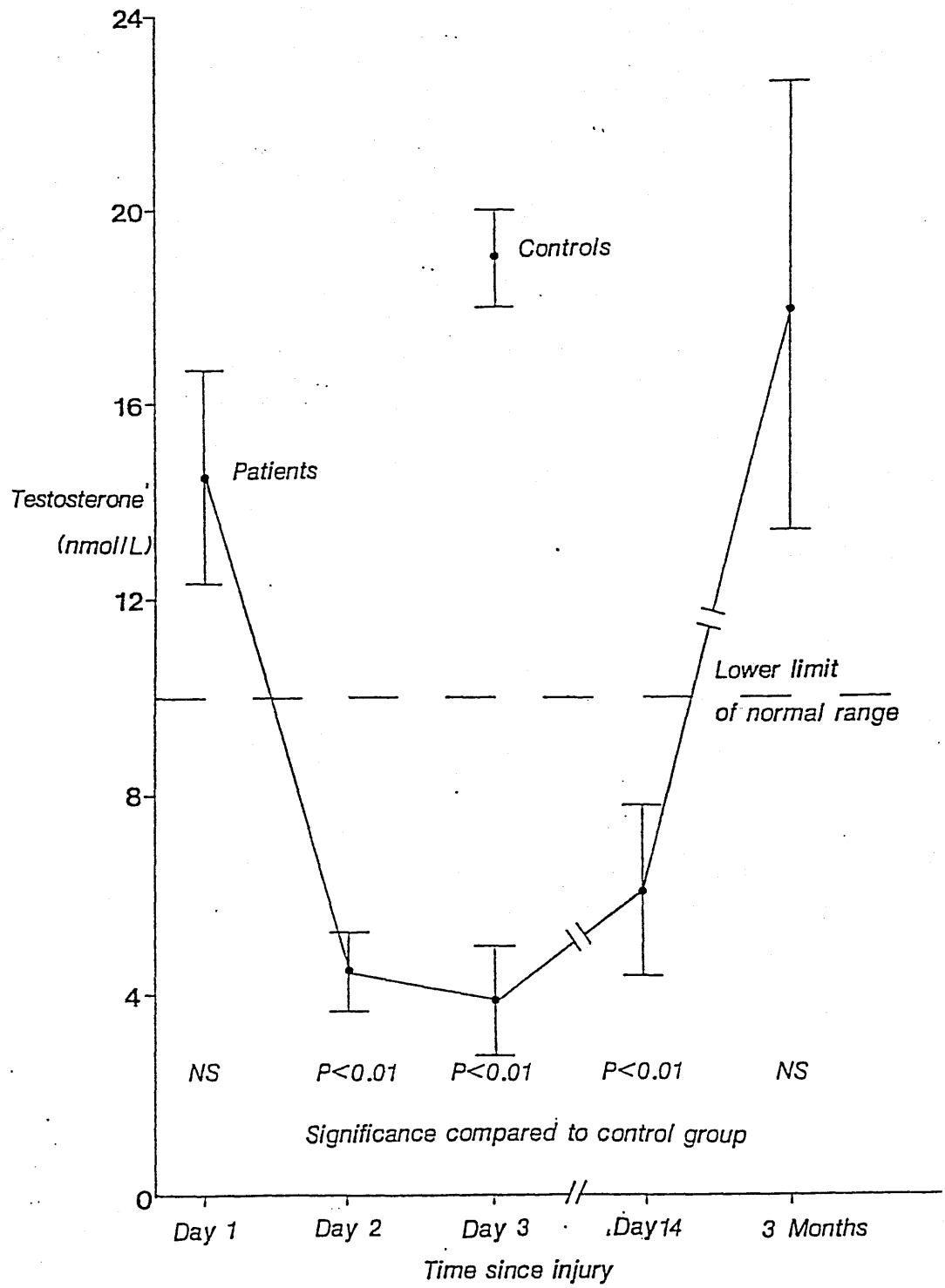
All blood sampling, LH hormone assays and pulse analysis using the threshold method and the "detect" program were performed by myself.

Results

(1) Testosterone and time since injury (Fig 11)

As noted in the main study there was a significant fall in testosterone to subnormal levels after injury. The mean value was back within the normal range by 3-6 months. The levels on day 2, 3 and 10-14 were all

Figure 11 Testosterone and time since injury



significantly less than the day 1 and 3-6 month values (all $p < 0.01$) and the mean control value ($p < 0.01$).

(2) LH and time since injury (Fig 12)

The basal LH was highest on day 1 and was significantly greater than all subsequent patient values ($p < 0.01$), except the 3-6 month value. It just failed to reach a significantly greater level than the mean control value ($p < 0.06$). The patient's mean value then progressively fell to a nadir on day 4, followed by a gradual rise to the 3-6 month value. The values from day 2 to day 10-14 were all significantly less than the control mean (all $p < 0.01$). The 3-6 month value was similar to the control mean.

(3) Peak LH During Releasing Factor Stimulation Test (Table 30)

The pattern observed in the main study was repeated in these patients with the highest peak occurring on admission. Although the peak value was outside the normal range in 4 patients on admission the mean value was not significantly greater than the values after 1 week or 3-6 months.

(4) Basal LH During Pulsatility Study

Each subject had 55-60 samples taken during the 6 hours of the pulsatility study and their mean LH value was calculated (Table 31). The mean value was

Figure 12 LH and time since injury

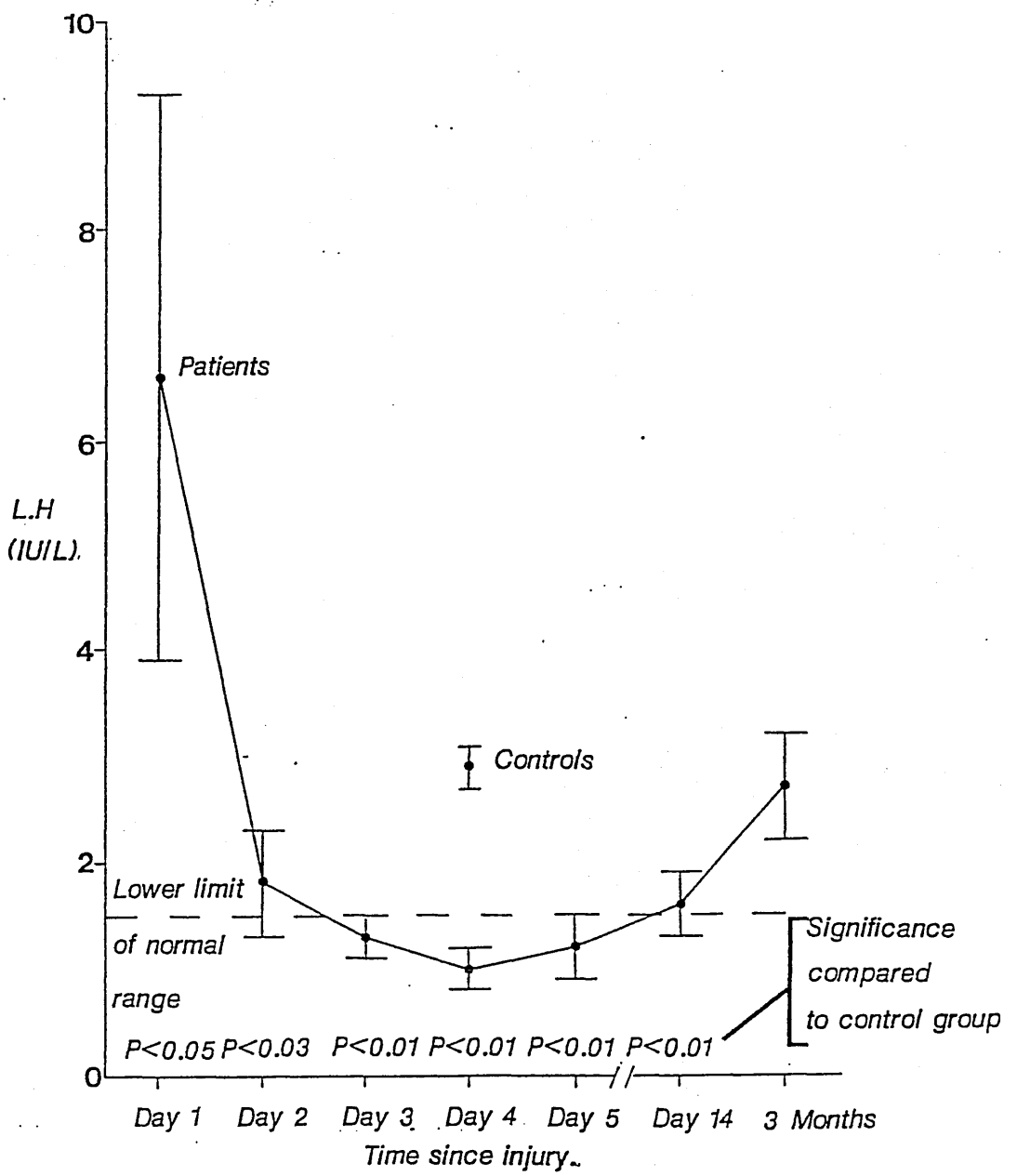


Table 30 PEAK LH (IU/L) DURING RF TEST

	Admission	Day 7-10	3-6 months
JF	56 IU/L	33 IU/L	22 IU/L
AW	50 "	30 "	17 "
RM	31 "	25 "	29 "
PW	35 "	12 "	18 "
GM	6 "	19 "	25 "
Mean ± SEM	36 ± 9	24 ± 4	22 ± 2

Table 31 MEAN LH DURING PULSATILITY STUDY

Patients	Mean LH (IU/L)	Controls	Mean LH (IU/L)
JF	2.63	1	2.39
AW	0.59	2	2.75
RM	0.83	3	2.10
PW	2.23	4	2.50
GM	1.06	5	3.28
		6	2.68
Mean ± SEM	1.47 ± 0.4	Mean ± SEM	2.62 ± 0.16

significantly greater in the controls ($p < 0.01$), with all 6 control subjects having mean values greater than 2 IU/L compared to only 2 of the head injury patients.

(4) Pulse Frequency (Table 32A + B)

Pulses were identified by the fixed threshold method and the detect program and the periodicity of the pulses was determined by time series analysis. All 3 methods of pulse analysis demonstrated that there was no significant difference in pulse frequency between the head-injured patients and the control subjects. Although the detect program could only be used to analyse the first 4 hours of results, whereas the fixed threshold method could be applied to the full 6 hours of results, the detect program consistently identified more pulses in both groups of subjects. It can be seen that a "pulse frequency" derived from the time series analysis method, by dividing the duration of the study in mins by the estimated periodicities, would produce values inbetween the fixed threshold and detect methods.

(5) Pulse Amplitude (Table 33 + Fig 13)

The pulse amplitude was significantly smaller in the head-injured patients by both the fixed threshold method ($p < 0.001$) and the detect method ($p < 0.02$). The time series analysis method was not adapted to measure pulse amplitude. The detect program recorded

Table 32A PULSE IDENTIFICATION IN PATIENTS

Patient	Fixed Threshold (Pulses/6hrs)	Detect (pulses/4hrs)	Time Series Analysis (periodicity in mins)
JF	2	5	100
AW	3	5	100
RM	3	5	100
PW	3	6	90
GM	2	5	80
Mean	2.6 ± 0.25	5.2 ± 0.2	94 ± 4

Table 32B PULSE IDENTIFICATION IN CONTROL SUBJECTS

Subject	Fixed Threshold	Detect	Time Series Analysis
1	2	4	90
2	3	6	100
3	4	4	100
4	2	4	80
5	5	4	85
6	4	5	90
Mean	3.3 ± 0.5	4.5 ± 0.3	91 ± 3

Figure 13 LH pulse amplitude in patients and control subjects

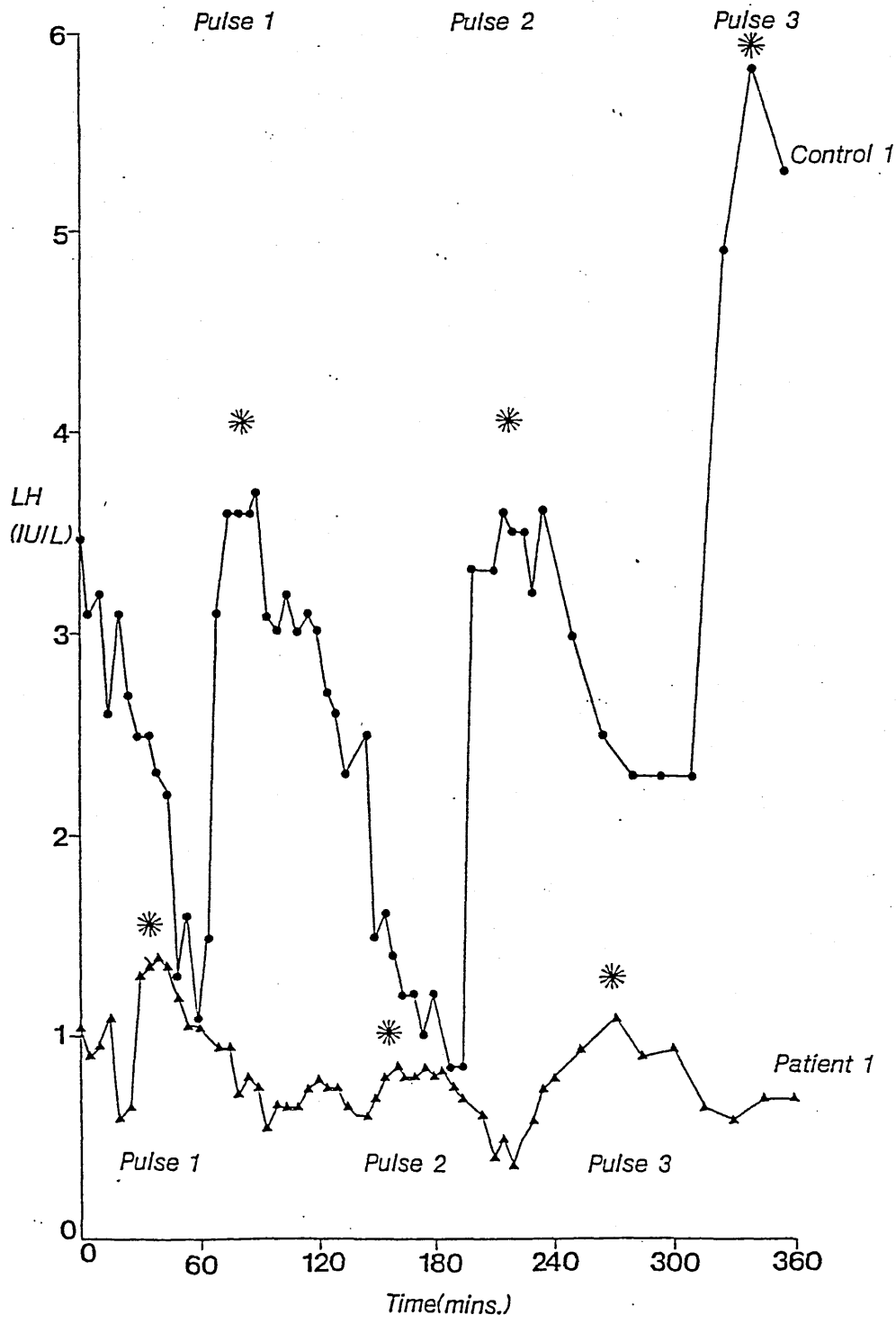


Table 33 MEAN PULSE AMPLITUDE (IU/L)

	PATIENTS			CONTROLS	
	Fixed Threshold	Detect		Fixed Threshold	Detect
JF	1.32	0.87	1	2.0	0.83
AW	0.29	0.21	2	2.3	1.07
RM	0.37	0.37	3	2.4	0.62
PW	0.80	0.57	4	2.3	1.03
GM	0.70	0.55	5	1.8	1.28
			6	1.5	0.66
Mean±SEM	0.7±0.2	0.51±0.1		2.05±0.1	0.92±0.1

pulse amplitudes in both control subjects and patients that were smaller than those obtained by the fixed threshold method. The detect program revealed that 54 % of pulses in the head-injured patients had an amplitude less than 0.3 IU/L, compared to only 12 % in the control subjects.

C H A P T E R 5

DISCUSSION

Stress Hormones

Thyroidal Axis

Gonadal Axis

Fatalities

Diabetes Insipidus

DISCUSSION

STRESS HORMONE SECTION

Three stress hormones were investigated in this study; cortisol, growth hormone and prolactin. Each hormone is initially discussed separately before a comparison is drawn between them.

Cortisol

The mean cortisol level was elevated shortly after injury, with the highest level occurring within 24 hours. Many of the values at this time were just below the mean of 1200 nmol/L attained after a few hours maximal stimulation with ACTH in normal subjects (Eik-Nes et al, 1954; Christy et al, 1955), suggesting that the adrenals were almost maximally stimulated. By 7-10 days the mean value was just within the normal range and after 3-6 months it was in the middle of the normal range, which is in keeping with previous workers who reported that 6-12 days after injury the level is at the upper limit of normal (Barton and Passingham, 1981), returning to the middle of the normal range by 2-3 weeks (Frayn et al, 1983). No sex difference has been reported for the cortisol response to injury and in this study similar levels were found in male and female survivors. Older patients (greater than 80 years old) have been reported to have a more sustained elevation in their serum cortisol concentration (Frayn

et al, 1983), although in this study no difference was noted at any stage between levels in younger subjects and the limited number of older subjects.

An important factor influencing the cortisol level is the severity of the injury. Although a positive correlation was found between the plasma cortisol concentration and injury severity in male survivors studied within 24 hours of injury, a significant negative correlation had developed by 1-3 days. One week later a positive correlation had become re-established. Thus our study demonstrates that there is a transient phase between the first to third day after injury when more severely injured patients have significantly lower cortisol levels than less severely injured. Our study is the only one to have examined the relationship between injury severity and cortisol levels more than 24 hours after injury in a large group of subjects and thus no other authors have observed the transient reversal in this relationship.

Most previous studies have observed a positive relationship between injury severity and several variables, including plasma cortisol concentrations (Stoner et al, 1977; Barton et al, 1987) and the incidence, magnitude and duration of the cortisol response (Steinbok and Thompson, 1979; Frayn et al, 1983). Two studies failed to detect any relationship between severity of injury and cortisol levels (King et al, 1970; Barton and Passingham, 1981), but in King's study lower cortisol levels were reported with less

severe injury, although this just failed to achieve significance and Barton and Passingham remarked that their finding of a lack of relationship with injury severity may have been due to the small number of patients in their study.

Although no other studies have reported the development of a negative correlation between injury severity and cortisol levels a few days after injury, two previous studies (Stoner et al, 1977; Barton et al, 1987) were able to identify a small subgroup of subjects with more severe injuries in whom there was a negative relationship within 24 hours of injury. Further evidence for lower cortisol levels in the more severely injured was reported by Meguid et al (1974), who observed that admission cortisol levels in a major trauma group were lower than those in a minor trauma group and by Carey et al (1971) who noted that plasma cortisol levels were lower than expected in severely injured battle casualties. A possible explanation for the lower cortisol levels in the more severely injured subjects could be reduced arterial perfusion of the adrenal cortex due to a fall in blood pressure. In our study although some of the more severely injured subjects (fatalities) had low cortisol levels, other severely injured subjects had high levels within 24 hours of injury. Thus a negative relationship was not detected in our group of most severely injured subjects at this early stage.

As one of the aims of this study was to detect any subjects who developed secondary adrenal failure a single random cortisol level would have been insufficient, particularly in follow-up tests several months after injury. Therefore, in order to assess the integrity of the pituitary-adrenal axis our patients had stimulation tests performed with CRH, on admission and during subsequent investigations. All but 7 of the 48 surviving patients had a basal cortisol level of greater than 500 nmol/L on admission, which was taken to represent the minimum adequate pituitary-adrenal stress response. Only 1 of these 7 patients with a low basal level also had an impaired cortisol response to CRH and he had probably received exogenous steroids. The remaining 6 subjects had less severe injuries and their admission to our unit was delayed, possibly permitting time for their cortisol level to fall to less than 500 nmol/L. Subsequently 5 of these 6 subjects had normal levels with an adequate response to stimulation with CRH. The 6th subject and 1 further subject were found to have levels less than 500 nmol/L, with an increment less than 150 nmol/L, after 3-6 months. However their cortisol responses to insulin hypoglycaemia were normal, indicating that in these 2 subjects CRH had not provided a sufficient stimulus to cortisol secretion. Therefore in the 48 surviving patients no cases of early or late secondary hypoadrenalism were identified.

At all times after injury there was a highly significant negative correlation between the basal cortisol level and the increment in response to CRH, a finding which has previously been reported in healthy subjects (Hermus et al, 1984).

Growth Hormone

The growth hormone (GH) response to injury was similar to the cortisol response, with the highest levels occurring within 24 hours. However very few survivors had levels greater than the upper limit of normal and any such elevations were transient and minimal, so that the mean basal level was within the normal range at all times. Even our subjects with the most severe injuries (the fatalities) rarely had elevated values and their mean level was similar to the survivors. Frayn et al (1984 b) noted that GH levels were elevated above the normal range if samples were taken within 1 hour of injury and there was a rapid fall in GH following this initial elevation. Thus the delay in our initial sampling, even in subjects studied within 24 hours of injury, could explain why the mean GH levels were within normal limits, although a significant fall in GH was still detected in male survivors when later tests were compared to the admission values. A similar pattern was apparent in the female survivors but did not achieve significance.

A correlation between injury severity and the extent of the elevation in GH might seem reasonable, but the only studies in patients with head injuries have found no such relationship (Rudman et al, 1977; King et al, 1981), although both studies had methodological faults (a small number of patients and a

delay in sampling). In contrast our largest group (male survivors) exhibited a strong correlation between injury severity and the basal GH level, from admission through to 1 week after injury. The relationship was different from that observed with cortisol, as there was a consistent positive correlation throughout the first week, without a reversal in the relationship after 1-3 days. In our 2 other groups (female survivors and fatalities) no correlation was present and this may have been because of the small numbers in each group.

Plasma GH levels after injury reflect the rate of GH synthesis and release from the anterior pituitary but more direct information on pituitary function can be obtained by performing dynamic tests of GH secretion. No previous studies have investigated the storage pool of GH after injury, although one study did report a paradoxical GH response to an intravenous glucose load shortly after head injury, suggesting abnormalities in the central control of GH secretion (King et al, 1981).

The response to stimulation with GHRH was extremely variable, as has been reported in normal subjects (Thorner et al, 1983; Grossman et al, 1984), with a wide range of peak levels at all times after injury. Both groups of survivors had their lowest response on admission, with the male subjects having a significantly lower response than the females. Subsequently there was no sex difference. Two studies have reported no sex difference in the GH response to

GHRH (Gelato et al, 1984; Hol et al, 1985), whereas one study recently observed a greater response in male subjects and suggested this was related to testosterone (Smals et al, 1986). On admission our male subjects had a poor GH response with a relatively higher testosterone concentration when compared to the testosterone level one week later, when the GH response was greater. This suggests that the testosterone concentration bore no relationship to the GH response in our study.

In contrast to cortisol, we observed that the GH increment in response to stimulation with its hypothalamic releasing factor was directly related to the basal GH level. However this relationship was only present for the first week after injury, during the period of maximum stress, and was no longer apparent after 3-6 months. Previous studies in which GHRH tests have been performed in healthy subjects and growth deficient subjects have not reported any correlation between the basal GH level and the increment in response to GHRH, although one study did report that subjects with a basal GH level less than 1 ng/ml had a significantly smaller response than those with a basal level greater than 1 ng/ml (Smals et al, 1986). In acromegalic subjects a strong correlation has been reported between the basal and peak GH levels after stimulation with GHRH (Smals et al, 1987). The changing relationship in our study may have arisen because following injury the dominant influence on the control

of GH synthesis will be stimulation by endogenous GHRH, with a reduction in the inhibitory role of somatostatin. Thus the higher plasma GH levels will directly reflect the increased rate of GH synthesis and secretion from the pituitary and, because the inhibitory mechanisms are switched off, the GH response to exogenous GHRH will be correlated to the plasma GH level. However after 3-6 months the inhibitory mechanisms will be functioning again and the relationship between the amount of GH released in response to exogenous GHRH and the basal GH level will be lost. Thus it appears that the correlation only exists when there is increased secretion, which could be due to stress or acromegaly.

The relationship between injury severity and the peak GH level was also examined and, as one might have expected, a significant correlation was found on admission, although the correlation coefficient just failed to achieve significance 1 week later.

During the period of the highest rate of GH synthesis, shortly after injury, when there is a strong relationship between the basal GH and its response to exogenous GHRH, the GH storage pool must be at its smallest, as the response to exogenous stimulation with GHRH was reduced during this period in all groups. At this stage plasma GH levels are highest and it is likely that a greater proportion of the GH storage pool is released with each pulse of endogenous GHRH, such that the pool becomes reduced in size. Later the plasma

GH levels fall, possibly because less GH is released in response to endogenous GHRH, and the GH pool re-accumulates. This would result in a larger GH response to the pharmacological dosage of GHRH in the exogenous stimulus, when compared to the admission test results. This may explain why the peak level in response to GHRH was significantly greater by 7-10 days and had increased even further after 3-6 months. Similarly the females had their smallest response to stimulation shortly after injury and their greatest response during convalescence. Thus when the basal GH level was highest the response to stimulation was least and as the basal GH level fell the response to stimulation increased.

Steroids can inhibit the GH response to stimulation (Hartog et al, 1964) and our study has demonstrated that the subjects cortisol levels were highest at the time of their reduced GH response to stimulation. However the strong correlation between the basal GH level and the amount of GH released from the storage pool in response to GHRH suggests that an additional explanation for the initial reduced response involving cortisol is not required.

After 3-6 months no survivors were considered to be GH deficient, although 1 patient continued to have a peak level less than 10 mU/L.

Prolactin

In this study the mean prolactin levels were elevated after head injury. Resting and stimulated PRL levels are known to be higher in females and in keeping with this all mean values after injury were significantly greater in the female group. Following injury the increase in basal levels was sustained for a considerably longer period than GH, with mean levels still outside the normal range after 7-10 days in both sexes. By 3-6 months the values had returned to within the normal limits. The time course suggests that after head injury prolactin remains elevated for a longer period than after surgery (McFarlane and Rosin, 1980) and is more in keeping with the prolonged rise observed after burn injury (Brizio-Molteni et al, 1984). The only study in which PRL was measured in head-injured subjects (King et al, 1981) was inconclusive, probably because of the small number of subjects and the short duration of the study. PRL was measured for the first 3 days after injury in 6 male subjects and was elevated in 3 of them.

Despite the difference in time-course of the elevation compared to GH, the relationship between injury severity and PRL was identical to that for GH. A strong correlation existed between injury severity and the basal PRL level on admission in both groups of survivors and was still present in the males (the larger group) one week later. As for GH no relationship existed several months later when the patients were

convalescing. Although a correlation between injury severity and PRL level has not previously been investigated, Noel et al (1972) reported that subjects undergoing major surgery had higher PRL levels than subjects having gastroscopy or proctoscopy. Our most severely injured subjects (the fatalities) did not have a greater PRL level than the survivors, possibly indicating impaired pituitary PRL secretion in the fatalities.

Further evidence for abnormalities in PRL secretion after injury came from the dynamic studies. There have been no previous reports on the prolactin response to stimulation in stressed patients. We found that females had the greatest response and their peak level after stimulation remained virtually constant at the various time points after injury. However in male survivors the peak level within 24 hours of injury was significantly reduced compared to later stages. The mechanism for this initial reduction may be the same as for GH, with a poor response to TRH because the PRL storage pool has already been discharged following injury. However as endogenous TRH is not thought to be a physiological mediator of PRL synthesis or secretion (Delitala et al, 1987), stimulation tests with TRH may be difficult to interpret because exogenous TRH may have incomplete access to the PRL storage pool after injury. Increased cortisol levels on admission have been suggested as a possible mechanism for the reduced GH response to GHRH, but the additional presence of a

reduced PRL response to TRH makes this unlikely, as cortisol is not known to have an inhibitory effect on PRL.

In survivors there was no relationship between the basal PRL level and the size of the increment in response to TRH during the first week after injury. However by 3-6 months a significant correlation had developed in both groups of survivors. Thus despite the similarities to GH with regard to injury severity and basal hormone level there was a completely different relationship during dynamic testing. As mentioned above this may have arisen because TRH is not a physiological mediator of PRL secretion and thus may have limited access to the PRL storage pool after injury. However despite these reservations the peak PRL level in response to TRH did have a significant relationship to injury severity during the first week after injury, with the correlation coefficients even greater than those for basal PRL.

In female subjects the clinical associations of an elevated PRL level include galactorrhoea and amenorrhoea, but as yet there have been few studies of PRL after injury which have also examined these features. Hyperprolactinaemia has been said to occur frequently after injury to the chest wall in female subjects (Besser and Thorner, 1976) and there have been several reports of galactorrhoea after surgery to the chest wall (Salkin and Davis, 1949; Grossman et al, 1950; Berger et al, 1966). In a further report a

subject who had burns to the chest wall developed amenorrhoea and galactorrhoea and the elevated prolactin levels were reduced to normal by bromocriptine (Morley et al, 1977). More recent work (MacFarlane and Rosin, 1980) has suggested that in galactorrhoea induced by chest wall injury, the elevation in PRL is short-lived, but is able to initiate lactation, which continues despite the presence of normal PRL levels.

In our study 3 of the 8 pre-menopausal females who were reviewed after 3-6 months were amenorrhoeic and a further 3 had experienced a menstrual upset (missed period, irregular cycle), although none were found to have galactorrhoea. All but 1 of these 8 subjects had a PRL level of greater than 700 mU/L after injury and they had elevated PRL levels for a longer duration than the subjects reported by MacFarlane and Rosin (1980), who developed galactorrhoea, following chest wall injuries. After 3-6 months only 1 patient continued to have a substantial elevation of her PRL level, which was probably due to her psychotropic medication, and she remained amenorrhoeic. Of the remaining 2 patients with amenorrhoea neither had a significant elevation of their PRL level after 3-6 months, although both had values greater than 1000 mU/L one week after injury. A similar pattern was present in 2 of the 3 patients who had experienced a transient menstrual upset, with a substantial elevation one week after injury but only a minimal elevation after 3-6 months. The transient

increase in PRL concentration during the first week after injury may have interfered with gonadotrophin regulation at the hypothalamic or pituitary level, resulting in a more prolonged menstrual upset (Bouchard et al, 1985). However mechanisms other than an elevation in PRL could have been responsible, because none of the 5 male subjects who were hypogonadal after 3-6 months had substantial elevations of their PRL concentrations at any stage. The only male subject with a large elevation after injury was receiving a short course of treatment with metoclopramide, which was probably responsible for the increase. When reviewed after 3-6 months he was no longer receiving this drug and his level was within the normal range and he had no hypogonadal symptoms.

Summary of the Cortisol, GH and PRL responses to injury

As expected the levels of the three stress hormones were greatest shortly after injury, at the time of maximum stress. Both cortisol and PRL were raised above the upper limit of normal on admission, whereas GH remained within the normal range. The increased rate of secretion of each hormone was maintained for at least 1 week, as their levels at this stage remained significantly greater than the 3-6 month values. In addition our study has demonstrated that the degree of elevation of each hormone on admission was significantly correlated to the severity of the head injury. However although GH and PRL levels were

positively correlated to the injury severity throughout the first week, cortisol exhibited a temporary reversal of this relationship 1-3 days after injury, indicating that at this stage more severely injured patients had lower cortisol levels.

Within 24 hours of injury the GH and PRL levels were significantly correlated, although neither were correlated to cortisol. When the cortisol levels fell in the more severely injured subjects after 1-3 days there was a significant negative relationship between the cortisol level and both GH and PRL.

Further differences between the three hormones became apparent during dynamic testing. The cortisol response to stimulation was negatively correlated to the basal cortisol level at all times after injury, whereas the GH response was positively correlated to its basal level during the first week and the PRL response was positively correlated to its basal level only after 3-6 months. Thus under conditions of stress the normal negative feedback of cortisol on ACTH synthesis and release must continue to operate, so that in the presence of high cortisol levels there is a reduced ACTH and cortisol response to exogenous CRH. In contrast during the period of maximum stress shortly after injury the stimulation to GH secretion overrides any possible negative feedback on its own synthesis and a temporary positive relationship is established between the basal GH and its response to GHRH. A third type of relationship is demonstrated by PRL, with a

transient loss of the normal positive correlation between PRL and its increment in response to TRH shortly after injury, possibly because of limited access of exogenous TRH to the PRL storage pool at this stage. By 3-6 months a positive relationship had become re-established. Thus the central control of each stress hormone is different after injury. The closest relationship appears to be between GH and PRL, although they have different responses during dynamic testing.

Despite the various changes in the stress hormone secretion described above there were few clinical sequelae in the survivors. Although 2 patients had subnormal cortisol responses to CRH after 3-6 months, they had normal responses to insulin hypoglycaemia and thus glucocorticoid deficiency was not apparent in any survivors. Whilst a reduced GH response to stimulation was frequently present on admission in the survivors, no significant abnormalities in GH secretion were noted after 3-6 months. The only clinical sequelae related to the stress hormones may have been due to hyperprolactinaemia, which was frequently found in the female survivors, and could have contributed to the amenorrhoea and menstrual upset observed in several of them.

THYROIDAL AXIS

Thyroidal hormone levels are known to fall in a variety of stressful conditions (Semple, 1986) and thus would be expected to decrease following major head injury. In our study subnormal T3 levels were observed more frequently than subnormal T4 levels and most subjects with a subnormal T4 level also had a subnormal T3 level. Stress did not disrupt the correlation between T3 and T4, which was present at all stages after injury. The lowest mean T3 level occurred on admission in all 3 groups of subjects and was subnormal. The male survivors continued to have a subnormal level 1 week later. The degree of the reduction in T3 concentration has previously been related to the severity of the surgical trauma, as well as the prognosis (Delitala et al, 1987) and this relationship was confirmed in our study. Combining the results from all subjects it was apparent that the T3 level was inversely related to the injury severity, both on admission and 1 week later. Consequently the fatalities had the lowest mean level, although it was not significantly less than the other 2 groups. A similar pattern was apparent for T4, with a significantly reduced value on admission, although it remained within normal limits. The T4 did not remain low for as long as T3 and by 1 week there was a rebound increase in T4, such that in both groups of survivors it was higher than the 3-6 month level (but not significantly). This transient increase in T4 was

associated with a decreased TSH response to TRH one week after injury.

The difference in time course between the recovery of the T3 and T4 concentrations indicates that the suggested impairment in peripheral deiodination of T4 to T3 after injury takes longer to recover than the decreased T4 secretion and binding inhibition of T4, which are responsible for the low T4. As for T3 our study demonstrated an inverse relationship between T4 and injury severity on admission and 1 week later. Thus, as expected, the fatalities had a lower T4 than the 2 groups of survivors.

Most studies of the thyroidal axis after injury have reported normal TSH levels (Elliott and Alberti, 1983) and a recent paper examining TSH levels after head injury confirmed that values remained within the normal range (King et al, 1981). Although Rudman et al (1977) reported "suprahypophyseal hypothyroidism" with low TSH levels their results should be interpreted with caution as all seven patients received large doses (24 mg) of dexamethasone daily, a drug which is known to suppress the pituitary-thyroid axis. Furthermore during their statistical analysis all TSH values less than the lower limit of the assay (1 uU/ml) were considered to be zero, which resulted in mean values less than the lower limit of the assay. However the common feature of all these studies was that the TSH level failed to rise despite low concentrations of thyroidal hormones,

indicating central abnormalities in the control of TSH secretion.

Accurate information on TSH levels in non-thyroidal illness has only become available with the recent development of more sensitive TSH assays. Wehmann et al (1985) and Hamblin et al (1986), examining critically ill patients, have reported subnormal TSH levels in conjunction with low thyroidal hormones. As the TSH levels recovered the thyroidal hormones increased back to normal. Our results from the male survivors confirm this finding, as a significant reduction in TSH with low thyroidal hormone levels was observed on admission, with subsequent return of the thyroidal hormone levels back to normal as the TSH levels recovered. Further evidence that there is a central defect in TSH secretion after head injury is provided by the inverse relationship observed between the peak TSH level on admission and the injury severity (a relationship with basal TSH levels could not be investigated because of the lack of a lower limit to the TSH assay). Thus hypothalamo-pituitary control of the thyroid axis is upset by head injury and may be responsible for the observed subnormal thyroidal hormone concentrations.

Although no relationship was present between the basal TSH level and the thyroidal hormone concentrations on admission, a significant positive correlation had developed with T3 after 1 week and was present with both thyroidal hormones after 3-6 months.

Dynamic stimulation tests of TSH have not previously been performed in injured patients, although in healthy subjects there is a direct relationship between the basal TSH level and the increment in response to TRH (Erfurth et al, 1984). In the female survivors a strong correlation was present at all times after injury and in male survivors after 1 week and 3-6 months. Examination of individual cases in which the new, more sensitive TSH assay was used also suggests that the normal relationship between TSH and its increment appears to have been maintained after injury. Three of the 4 patients with subnormal TSH responses to TRH shortly after injury had basal TSH levels determined by the new assay and their values were grossly reduced (all less than 0.2 mU/L) - the fourth patient had a basal level < 1 mU/L by the old assay. During subsequent tests although 2 of the patients still had subnormal TSH responses when their basal levels were just within normal limits (0.6 + 0.7 mU/L), all remaining TRH tests returned to normal when the basal TSH had risen back into the normal range.

Persistent abnormalities in the thyroidal axis were unusual with no survivors developing secondary hypothyroidism. One patient was found to have undiagnosed primary hypothyroidism and was commenced on treatment. An exaggerated TSH response to stimulation, suggestive of central hypothyroidism (Faglia et al, 1973) or subclinical hypothyroidism was observed in 1 female subject during all 3 of her tests.

Our study has confirmed that a reduction in thyroidal hormone concentrations occurs after injury and that the extent of the fall is dependent on the injury severity. In addition evidence of a reduction in TSH levels was presented and it has been suggested that central abnormalities may contribute to the fall in thyroidal hormone levels after injury.

GONADAL AXIS

There have been several studies on the effects of injury on the gonadal axis in man and in all cases a transient fall in total testosterone has been reported (Nakashima et al, 1975; Rudman et al, 1977; Wang et al, 1978 b; Vogel et al, 1985; Woolf et al, 1985; Woolf et al, 1986). We also observed a rapid and substantial fall in testosterone after head injury, with the nadir occurring between 1-3 days. The mean level remained suppressed one week later but it was back in the normal range when the convalescent tests were performed after 3-6 months. However 5 of the male survivors, who had made a complete neurological recovery, were found to have persistently low gonadal steroid concentrations after 3-6 months and they had all developed hypogonadal symptoms. They had no significant previous ill-health and had not sustained gonadal injury. This long duration of symptoms has not previously been reported and is in contrast to Rudman et al (1977) who observed that testosterone returned towards the normal range when consciousness was regained. Although Woolf et al (1985) observed that testosterone levels remained low beyond the period of coma he found that they returned to normal once the patients were ambulatory and he did not report any patients with prolonged hypogonadism.

In previous studies attempts have been made to relate the fall in testosterone to the severity of the

injury, with varying results. Woolf et al (1985) initially reported no relationship but in a subsequent paper (Woolf et al, 1986 he found that the fall in testosterone by day 4 was greater in patients with more severe injuries. Rudman et al (1977) reported that the fall in testosterone was significantly related to the depth of coma, although he excluded 2 of his 7 patients in this analysis. Our study has demonstrated a significant inverse relationship between injury severity and the testosterone concentration on admission.

In order to confirm that the fall in total testosterone concentration was real and not due to changes in binding proteins the free testosterone concentration was determined in a proportion of subjects. It fell to very low levels and was strongly correlated to the total testosterone concentration. No direct measurements of free testosterone have previously been made, although the percentage of dialysable (Goussis et al, 1983) and ultrafilterable (Woolf et al, 1985) testosterone were noted to be unchanged during the fall in testosterone after injury.

Female patients in our study had a similar pattern with a significant fall in oestradiol concentration occurring after injury. The lowest mean level, which was recorded after 1 week, was in the post-menopausal range and 3 of our subjects, who were amenorrhoeic when reviewed after 3-6 months, continued to have low oestradiol concentrations. Thus our results are at

variance with Woolf et al (1985), who reported that the abnormalities only persisted for 7 days in women of reproductive age. The fall in oestradiol concentration was independent of the stage of the menstrual cycle, as previously noted by Woolf et al (1985). In this small group of subjects no relationship between the oestradiol concentration and injury severity was found. Combining the results from male and female survivors, 8 of the 31 survivors tested after 3-6 months had prolonged hypogonadism.

In order to determine whether abnormalities in central control were responsible for the fall in gonadal steroid concentration the basal gonadotrophin levels were measured. In male survivors a significant decrease from the admission values occurred in both FSH and LH after 1-3 days and remained low 1 week later, with recovery by 3-6 months. At all stages after injury the strong correlation between basal FSH and LH was maintained. A similar pattern with a significant fall in FSH and LH during the first week after injury has previously been observed (Rudman et al, 1977; King et al, 1981; Woolf et al, 1985; Woolf et al, 1986). No fall in gonadotrophin levels was found in the small group of female patients in our study and this may have arisen because few members of this group were studied within 24 hours of injury. Woolf et al (1985) observed a significant fall in pre and postmenopausal women. The lack of a compensatory rise in the basal gonadotrophin concentration in both groups of survivors during the

period of low gonadal steroid concentration, confirms that there is disturbance of the central control of gonadotrophin secretion after head injury.

At the time of the nadir in basal and peak FSH 1 week after injury, both indices were negatively correlated to injury severity. In contrast no correlation was found between LH and injury severity at this stage, although a significant negative correlation between both basal and peak LH and injury severity had developed after 3-6 months in the female survivors. Such a prolonged effect of injury on hormone concentration seems unlikely but menstrual irregularities were common, even at this late stage and as injury severity was correlated to both basal and peak LH and just failed to achieve significance with basal FSH the relationship may be genuine.

Woolf et al (1985) suggested that the first abnormality to develop was the fall in testosterone concentration and this was independent of the gonadotrophin concentration. Our results support his first suggestion, as within 24 hours of injury 7 subjects had a subnormal testosterone concentration but only 3 of them had developed a subnormal LH level. However his second suggestion is refuted by this study, as a highly significant correlation was found between the testosterone and LH levels on admission in the male survivors. This indicates that after head injury the fall in testosterone concentration must be faster than LH, while remaining correlated to it. This could arise

because of a relatively greater reduction in testosterone secretion or a faster metabolic degradation rate for testosterone.

Dynamic studies of gonadotrophin secretion were performed and a greatly exaggerated LH response to GnRH was observed on admission in both male and female patients and the peak level remained outside the normal range 1 week later in the male subjects. The FSH response was also exaggerated within 24 hours of injury in the male survivors, although it had returned to within the normal range on subsequent testing. In contrast to our results Woolf et al (1985) and Rudman et al (1977) reported normal gonadotrophin responses to GnRH in a small group of patients (9 in total). However their patients had been tested several days after admission, thereby missing the time when we observed the maximal response, and they were receiving dexamethasone, which is known to suppress the gonadal axis. Four of the 8 subjects (5 male, 3 female) with prolonged hypogonadism in our study continued to have an exaggerated LH response to stimulation after 3-6 months.

On admission, during the period of the greatest response, a highly significant correlation was present between the basal gonadotrophin level and the increment in response to GnRH. However in subsequent tests this relationship was lost. This pattern is similar to that observed with GH and suggests that inhibitory influences on FSH and LH secretion are suppressed after

injury, permitting a direct relationship between the basal gonadotrophin levels and their responses to GnRH.

Our observations on head injured patients do not agree with any of the recognised hormonal patterns occuring in hypogonadism. In primary hypogonadism a low testosterone is accompanied by elevated gonadotrophin levels and an exaggerated response to GnRH, whereas in secondary hypogonadism low testosterone occurs in conjunction with low to normal gonadotrophin levels and an absent or delayed response to GnRH. Our patients differed in that while testosterone levels were low and the basal gonadotrophin levels fell there was an exaggerated response to GnRH.

In order to provide further information on the central abnormalities responsible for this unique pattern the pulsatile secretion of LH was investigated in 5 male survivors. Three different methods of pulse analysis were used and each demonstrated that there was no difference in LH pulse frequency between the head-injured subjects and the controls. Thus, as there is a one to one relationship between endogenous GnRH pulses and LH pulses (Clarke and Cummins, 1982), the hypothalamic pulse generator must be firing at its normal frequency. However the 2 methods of pulse analysis which were able to measure pulse amplitude demonstrated a significant reduction in pulse amplitude in the head-injured subjects. This could mean that there is a reduced amount of endogenous GnRH in each pulse secreted by the hypothalamus, which could be due

to dysfunction in the hypothalamus or at a higher level. Alternatively the hypothalamus and higher centres could be functioning normally with endogenous GnRH secreted in normal amounts at a normal frequency, with the defect occurring in the pituitary. A possible pituitary defect could be down-regulation of the pituitary GnRH receptors. Whatever the mechanism the final result appears to be impaired endogenous secretion of the gonadotrophins but continued synthesis. The defect in secretion would produce a fall in both the gonadotrophin and gonadal steroid concentrations and the continued synthesis would explain the exaggerated gonadotrophin response to exogenous GnRH, which at such a high dosage might be able to overcome the block to gonadotrophin release.

There are several factors which may have had an influence on the development of the central gonadal axis dysfunction. Apart from physical damage to the hypothalamus or pituitary, alternative explanations for deficient gonadotrophin pulsatile secretion may be increased activity of the opioidergic system, which is an important modulator of the hypothalamic pulse generator (Moult et al, 1981; Ellingboe et al, 1982) and increased adrenergic tone which may act directly (Woolf et al, 1986) or modulate the opioid influence on gonadotrophin release (Kalra and Crowley, 1982). Although hyperprolactinaemia can also result in hypogonadism, possibly by diminishing pulsatile GnRH release (Bouchard et al, 1985), our patients

(particularly the males) had relatively small elevations of their serum prolactin levels.

Acute administration of opiate drugs can result in a fall of basal LH and testosterone concentrations, with the decrease dependent on the potency of the opiate (Cicero et al, 1977 a). As many of our patients were treated with opiate analgesics this therapy may have contributed to the fall in LH and testosterone. However our subjects also had a fall in FSH, which has not been observed after opiate administration (Mirin et al, 1976) and despite the difference in potencies of the 2 analgesics used in our study there was no significant difference in any of the hormone levels between the 2 groups. Furthermore animal experiments have shown that the LH response to GnRH (and the pituitary content of LH) is not altered by morphine administration (Cicero et al, 1977 b). Thiopentone anaesthesia produces no change in LH concentration although a fall in testosterone has been reported (Salo, 1982). As the mean hormone levels in our ventilated and unventilated patients were similar, thiopentone is unlikely to have had an important contribution to the observed changes.

The exaggerated gonadotrophin response is unlikely to be due to interaction between the hypothalamic releasing factors, as 3 recent studies have reported no potentiation of LH release after administration of combinations of the releasing factors (Sheldon et al, 1985; Looij et al, 1986; Sandler et al, 1986).

Similarly, it is unlikely to be due to a concurrently administered drug, as patients treated with different classes of analgesics and antibiotics had an exaggerated response.

The finding that a substantial number of patients are symptomatically hypogonadal several months after severe head injury and that this is confirmed by the presence of low gonadal steroid concentrations is of practical importance and possibly prognostic significance. In our review of post-traumatic hypopituitarism it was observed that the symptoms of hypogonadism preceded the diagnosis of panhypopituitarism by months to years (Edwards and Clark, 1986). Therefore careful review of these patients has been arranged to determine if the gonadal axis dysfunction is the forerunner of panhypopituitarism. Analysis of the endocrine and injury data failed to identify any risk factors which could predict the subsequent development of prolonged hypogonadism.

FATALITIES

Endocrine Findings, Histopathological Study, Endocrine-Histological Comparison and Prognostic Indicators

Endocrine Findings

Cortisol

Major abnormalities in stress hormone secretion were found in the group of 12 fatalities. The most serious complication was glucocorticoid deficiency, which was present in 4 subjects on admission and had developed in a further subject 1 week later. Death occurred shortly after injury in the 4 subjects with glucocorticoid deficiency on admission and the results of the releasing factor test were only available pre-mortem in 1 of these cases. He was commenced on hydrocortisone but was pronounced brain stem dead 2 hours later. These 4 subjects had such severe brain injury that survival was most unlikely even with replacement therapy. The fifth subject, who had a normal cortisol response on admission, had received a 3 day course of dexamethasone after his first releasing factor test but developed a severe rise in intracranial pressure on the 7th day after injury and was pronounced brain stem dead shortly after completion of the second releasing factor test. Thus again it is unlikely that replacement therapy would have affected his outcome.

The results in this subject are completely different from a head-injured patient reported by

Steinbok and Thompson (1979) who was noted to have breakthrough of his cortisol levels when dexamethasone was reduced to 4 mg/day, a dose which is normally suppressive. Our subject may have developed secondary hypoadrenalism between his first and second tests and was thereby unable to mount such a response. Our results also disagree with a report by Carey et al (1971), who suggested that cortisol levels continue to rise in fatally injured subjects until death.

Growth Hormone

On admission GH levels were similar to those in the male survivors. Although 4 fatalities had virtually no GH response to stimulation, with peak levels < 2 mU/L, this may not have reflected complete destuction of the somatotrophes, as several survivors had a similar response on admission but a normal response on retesting.

Carey et al (1971) also reported a continued increase in GH, to very high levels, in two fatally injured patients. However only one of our 12 fatalities had a substantial elevation of their GH level on admission (28 mU/L) and neither of the 2 fatalities who were retested 1 week later (shortly before their deaths) had elevated levels.

Prolactin

Although the basal level was similar to that in the male survivors, 7 of the fatalities had either no PRL response or a subnormal response to stimulation with TRH, resulting in a substantially lower peak level. Three of these subjects also had a low basal level, suggesting that there was destruction of their lactotrophes and possibly their anterior pituitary glands.

Thyroidal Axis

As expected thyroidal abnormalities were particularly common in the fatalities, with 9 subjects having a subnormal T3 level and 5 having a subnormal T4. In 6 subjects the T3 level was less than the lower limit of the T3 assay. Subnormal TSH responses to TRH were also frequently found in this group (9 cases). One fatality had results compatible with central hypothyroidism (Faglia et al, 1973).

Gonadal Axis

The basal FSH and LH levels were greater than those found in the survivors and the LH response to stimulation was reduced, indicating that the LH storage pool had been diminished while maintaining the higher basal level. In contrast to the 3 stress hormones measured in this study, the gonadotrophins were found to be significantly greater in the fatalities when

compared to the survivors. Thus with very severe injury the stimulus to gonadotrophin secretion must override the negative influences observed in less severely injured subjects. This may explain why the testosterone concentration was significantly greater in the fatalities and, unlike the survivors, was not negatively correlated to injury severity.

Histopathological Study

Although pituitary and hypothalamic damage have long been recognised after fatal head injury and may contribute to the fatal outcome (Daniel and Treip, 1961 and 1966; Harper et al, 1986), pituitary function has never been assessed in such a group. In this study pituitary function was assessed in 12 subjects who died as a consequence of their head injury, and subsequently their endocrine results were related to the histological findings in the hypothalamus and pituitary.

The histological changes observed in the anterior pituitary were similar to those previously reported (Daniel et al, 1959 b; Daniel and Treip, 1961; Ceballos, 1966; Kornblum and Fisher, 1969; Harper et al, 1986) and included large centrally situated infarcts with a small surviving rim of variable thickness. The occurrence of large anterior pituitary infarctions in 9 of the 10 pituitary glands available for histological examination was considerably greater than the incidence in the above studies. This

difference may have arisen because our subjects had more severe head injuries, as all 12 died within 1 week of injury, whereas other studies included less severely injured subjects, who died several months after injury.

Hypothalamic damage was also frequently observed in our subjects, with petechial haemorrhages or small infarcts located in the paraventricular and supraoptic nuclei, median eminence and upper stalk, which is similar to the findings in previous studies (Treip, 1970; Crompton, 1971). Only 1 of our subjects had stalk section and this is in keeping with the low incidence reported by Ceballos (1966) and Harper et al (1986).

Anterior pituitary necrosis develops because of an interruption of blood flow in the hypothalamo-hypophyseal portal vessels in the pituitary stalk. Although it was initially suggested by Daniel and Treip (1961) that stalk transection was the responsible mechanism it is apparent from our study and other recent papers that stalk transection is infrequent and it is more likely that compression of stalk portal vessels on the diaphragma sella due to post-injury pituitary swelling and intracerebral oedema is responsible (Kornblum and Fisher, 1969; Harper et al, 1986). All 12 of our subjects had evidence of gross cerebral oedema on their CT scans, with obliteration of the lateral ventricles and perimesencephalic cisterns and flattening of the cortical sulci, and at postmortem, their brains were described as swollen and oedematous, with cerebellar coning frequently present.

Thus compression of the stalk vessels seems likely in these circumstances.

Harper et al (1986) reported a high incidence of fracture of the base of the skull in subjects with infarction of the anterior lobe and Daniel and Treip (1966) stated that a basal fracture was one of the two consistent clinical findings in such cases, the other being prolonged coma disproportionate to the severity of the head injury. However in this study there was no relationship between the histological changes and the site of skull fracture, as large pituitary infarcts were present in subjects with frontal, parietal and basal fractures and in 1 subject with no fracture. In addition the direction of the injuring force did not appear important as similar pituitary damage was observed in the 6 subjects whose impact was predominantly in the antero-posterior plane when compared to the 6 subjects injured by a lateral force.

It has also been suggested that hypotension and anoxia after injury may be responsible for the massive anterior pituitary infarction (Orthner and Mayer (1967). However all our subjects were maintained on a ventilator with their gas exchange carefully monitored and, as many of our fatalities were organ donors, blood pressure was carefully controlled.

Thus in our cases massive pituitary infarction was not due to hypotension or hypoxia and was independent of the direction of the injuring force or the presence of a skull fracture. It seems more likely that the

severity of the injury and the consequent intracerebral oedema, by producing stalk compression, are the determinants of the resulting pituitary necrosis.

Endocrine-Histological Comparison

Previous histological studies have not been able to compare their findings with the premortem endocrine results. Our finding of multiple hormone deficiencies in 6 of the cases with large pituitary infarcts is not surprising, but a further 3 cases had virtually normal dynamic tests. This may have arisen because these 3 subjects survived for 4-5 days after their endocrine tests were performed and thus may have developed pituitary infarction (possibly with endocrine abnormalities) at this late stage, during the period when their intracranial pressure was rising. The subject with pituitary stalk transection had no hormone response to stimulation, presumably because the blood supply to the anterior pituitary must have been completely severed.

The finding of most clinical relevance was that 5 subjects were glucocorticoid deficient. This occurred in 3 subjects with large pituitary infarcts, the subject with stalk transection and one case in which the pituitary was unavailable but the hypothalamus had infarction of the median eminence. Apart from the case with stalk transection similar histology was observed in other subjects but was not accompanied by glucocorticoid deficiency.

Immunocytochemical staining for ACTH, GH, PRL and TSH was generally positive in all subjects and was not reduced in patients with subnormal hormone levels or impaired hormone responses to releasing factor stimulation. However staining for LH was negative in virtually all fatalities and clearly different from the staining produced in control subjects. This is in keeping with the endocrine results for LH, which suggested a reduction in the LH storage pool. A similar reduction may have occurred to the GH and PRL storage pools, as elevated basal levels on admission were associated with a reduced response to stimulation, but this was not apparent from the immunocytochemical staining.

Prognostic Indicators

Our study has identified several endocrine changes associated with a poor prognosis. Glucocorticoid insufficiency was not demonstrated in any survivors during the first week after injury, but occurred in 5 fatalities. Similarly a deficient PRL response was present in 6 fatalities but not observed in any survivors.

There were several other endocrine changes suggestive of a poor prognosis. A reduced TSH response to TRH was the most frequent abnormality in the fatalities (9 cases) but was also present in some survivors. Analysis of mean levels demonstrated that T4 was lower in fatalities (T3 just failed to achieve

significance), whereas FSH, LH and testosterone levels were significantly higher in fatalities.

DIABETES INSIPIDUS

Diabetes insipidus (DI) has long been recognised as a complication of head injury (Rowntree, 1924) and it is said to be the most common hypothalamic disorder following trauma (Porter and Miller, 1948). However the two largest studies reported a low incidence, with 4 cases out of 2500 head injured subjects in Pickles (1947) series and 13 cases out of 5000 non-fatal closed head injuried in the study by Porter and Miller (1948). The incidence in our study in the survivors was 2 out of 48 subjects which is 15-25 times greater than the previous two studies. This substantial increase may have arisen because the 2 large studies were reported 40 years ago and since then there have been considerable advances in intensive care therapy, such that severely head-injured subjects, who are more likely to develop DI (Porter and Miller, 1948; Verbalis et al, 1985) are now surviving and subsequently developing it. There may also be better recognition of this complication because of an increased awareness. There have been no previous studies of DI complicating fatal head injury. The high incidence on this study (5 of 12 cases) confirms the association with severity of injury.

It has been suggested that the lesion responsible for the develoment of DI is most commonly in the pituitary stalk and occurs due to stretching of the relatively fixed stalk by the displaced brain at the time of injury (Porter and Miller, 1948). Animal

experiments (Magoun et al, 1939; Pickford and Ritchie, 1945) and studies in humans who have had their pituitary stalk sectioned (Lispett et al, 1956) have demonstrated that the develoment of permanent DI is dependent on the number of surviving ADH secreting neurons and if less that 10-20% remain viable then permanent DI will occur (Verbalis et al, 1985). Thus in our 3 subjects (2 survivors, 1 fatality) with transient DI it is likely that more than 20% of the ADH secreting cells survived and, once the inflammatory oedema had settled, ADH secretion could recommence with resolution of the DI.

The direction of the injuring force which is most likely to produce the stalk lesion appears to be in the antero-posterior plane, as 15 of Porter and Miller's 18 subjects and 6 of our 7 cases had frontal or occipital injuries.

The onset of DI in our subjects varied between 12 hours to 5 days after injury, which is similar to previous studies. The onset was abrupt in each subject and none had the occasionally reported triphasic pattern (Verbalis et al, 1985), in which an initial phase of DI is followed by a transient antidiuretic phase before the eventual return of DI.

Anterior pituitary dysfunction has been reported in association with DI but its frequency is uncertain. Barreca et al (1980) reported defective anterior pituitary hormone secretion in 8 out of 10 subjects, with GH and TSH most commonly involved and Verbalis et

al (1985) observed deficient TSH and ACTH secretion in 40% and 36% of subjects respectively. However neither study states how the hormone response was deemed to be deficient and the number of patients that actually required replacement therapy is not recorded. In contrast Porter and Miller (1948) observed only 1 case of anterior pituitary insufficiency out of 18 subjects with DI and Notman et al (1980) reported 1 subject with hypopituitarism out of 10 cases. Neither of our survivors had evidence of anterior pituitary dysfunction, although both had an elevated PRL level, which occurred shortly after injury and was probably due to the stress response rather than hypothalamic damage, as their PRL level was subsequently normal. However subnormal hormone responses to stimulation were found in 4 of the 5 fatalities with DI, which is presumably a consequence of their more severe injuries.

Thus DI was a relatively frequent occurrence in fatalities but was infrequent in the survivors. In contrast to previous studies disturbances of anterior pituitary function occurred considerably more often than the development of DI in both the survivors and fatalities.

SUMMARY OF RESULTS

Sixty subjects (48 male) were studied, of whom 12 died. Traffic accidents were responsible for 49 of the 60 injuries. A skull fracture was present in 32 subjects and 42 required assisted ventilation.

1. Gonadal Axis

The levels of total and free testosterone, oestradiol, basal FSH and basal LH fell significantly during the first 3 days after injury, when the LH and FSH responses to GnRH achieved their highest peak levels. This hormone pattern has not previously been reported in the gonadal axis. Persistent biochemical hypogonadism was found in 8 of 31 patients retested after 3-6 months, all of whom had clinical symptoms of hypogonadism. Analysis of the pulsatile release of LH shortly after injury demonstrated a reduced pulse amplitude with a normal pulse frequency, which may be due to either a hypothalamic or pituitary defect.

2. Thyroidal Axis

Basal TSH levels were frequently less than the lower limit of the assay within 24 hours of injury, in both survivors and fatalities and the TSH response to TRH was markedly reduced in fatalities. Thyroxine (T4) and tri-iodothyronine (T3) levels were reduced shortly after injury and were significantly lower in fatalities.

3. Cortisol Secretion

In the survivors cortisol levels were substantially elevated shortly after injury and gradually fell back into the normal range. However 5 fatalities were found to have low cortisol levels after injury (less than 400 nmol/L) and were considered to be glucocorticoid deficient.

4. Prolactin Secretion

Prolactin levels were elevated during the first week after injury. Female subjects had the highest basal levels and the greatest prolactin response to TRH, whereas fatalities had a significantly reduced response to TRH.

5. Growth Hormone Secretion

GH levels were highest on admission but remained within normal limits. There was a large variability in the GH response to GRH between patients. The response on admission was significantly reduced compared to later tests.

6. Response to Releasing Factor

At all stages after injury there was a significant negative relationship between the basal cortisol level and the size of the increment in response to CRH, whereas TSH remained positively correlated to its

increment throughout. During the first week after injury GH, FSH and LH were correlated to their increment but no relationship was present after 3-6 months. In contrast PRL was only correlated to its increment aftr 3-6 months.

7. Injury Severity and Hormone Concentrations

During the first week after injury the cortisol, GH and prolactin levels were positively correlated to injury severity (with a transient reversal in the cortisol relationship 1-3 days after injury). In contrast the testosterone, T3, T4 and the peak TSH level in response to TRH were negatively correlated to injury severity during this period. FSH levels became negatively correlated to injury severity at the end of the first week.

8. Histopathological Study

Large anterior pituitary infarcts were present in 9 of the 10 anterior pituitary glands studied. Damage to the hypothalamus was relatively mild, with occasional petechial haemorrhages in the paraventricular and supraoptic nuclei (6 cases), median eminence (3 cases) and the stalk (2 cases). Six of the 9 subjects with large pituitary infarcts had multiple hormone deficiences, including low levels of T3, T4 and cortisol and impaired pituitary hormone responses during the stimulation test.

9. Diabetes Insipidus

This occurred in 5 of the 12 fatalities but only 2 of the 48 survivors. The injuring force was in the antero-posterior direction in 6 of the 7 subjects with diabetes insipidus.

C O N C L U S I O N S

1. Endocrine function after head injury has not previously been studied. This project has demonstrated biochemical hypogonadism in virtually all subjects after injury, which persisted in a substantial proportion of subjects 3-6 months later. Further investigations demonstrated abnormalities in pulsatile LH secretion, indicating a central defect (hypothalamus or pituitary). Although impotence, loss of libido and amenorrhoea have been recognised after head injury they have previously been ascribed to psychological effects of the injury, whereas our study provides firm evidence of an endocrine cause and raises the possibility of therapeutic intervention.

2. In a review of the reported cases of post-traumatic hypopituitarism (including 6 of our own cases) we observed that hypogonadism often preceded subsequent panhypopituitarism. Thus our group of 8 patients with persistent hypogonadism may have an increased risk of subsequently developing post-traumatic hypopituitarism, although follow-up tests have not yet detected any further endocrine abnormalities.

3. Five of the 12 fatalities were found to be glucocorticoid deficient after injury and at post-mortem had extensive anterior pituitary necrosis,

stalk transection or hypothalamic infarction. Therefore glucocorticoid replacement therapy should be considered for patients who are considered to have the most severe injuries on clinical grounds, before the results of hormone investigations are available.

4. The stress hormone response was usually well preserved in survivors and the levels of cortisol, GH and PRL were positively correlated to the injury severity within 24 hours of injury. In contrast thyroidal and gonadal hormones were negatively correlated to injury severity. A sex difference was observed for prolactin, with female subjects having a greater release, which may have contributed to the oligo/amenorrhoea frequently observed in these subjects.

5. During the period of maximal stress positive correlations developed between GH, FSH and LH and the size of their increments, whereas PRL lost its normal positive relationship and the cortisol and TSH relationships were unchanged. Thus severe stress was able to override the physiological central inhibitory influences on GH, FSH and LH secretion and also disrupted central control of PRL secretion.

6. Diabetes insipidus was frequently observed in the fatalities, requiring treatment in 4 cases, but was rare (and temporary) in the survivors.

7. This study has identified a group of hormone measurements on admission which are indicators of a bad prognosis (low cortisol, T3 and T4 levels, reduced prolactin and TSH responses to stimulation with TRH and a lack of a reduction in FSH, LH and testosterone concentrations). Early identification of patients with such hormonal abnormalities may alert the clinician to the severity of the injury and target patients who require more intensive support.

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