Case No.	Age	Sex	Weight Before Treatment (in lb) and kg.)	Excess Weight (Expressed as % Standard Weight)	Blood-gas Analysis Before Treatment			Minimum Recorded *p*H Values and Associated Indices					
					*p*H	P_{CO_2} (mm.Hg)	Base Deficit (mEq/l.)	Days After Onset of Fast	Wt. Loss From Onset of Fast. (lb.)	Wt. Loss as % Pre-treatment Weight	*p*H	P_{CO_2} (mm.Hg)	Base Deficit (mEq/l.)
1	16	F	184 (83·4)	60	7·36	45	1	5	9	5	7·32	29	10
2	18	F	230 (104·3)	81	7·38	40	1	10	21	9	7·31	36	8
3	20	F	215 (97·5)	54	7·38	40	2	5	11	5	7·29	33	10
4	20	F	198 (89·8)	41	7·38	40	2	5	10	5	7·30	30	11
5	21	F	166 (75·2)	54	7·37	42	1	13	19	11	7·26	25	14
6	37	F	212 (96·1)	64	7·39	36	3	5	9	4	7·26	33	12
7	40	F	299 (135·6)	103	7·38	36	3	12	21	7	7·28	34	10
8	41	F	227 (102·9)	77	7·39	42	−1	6	16	7	7·28	29	12
9	44	M	229 (103·8)	42	7·40	33	3	10	38	16	7·30	30	11
10	50	F	186 (84·3)	43	7·37	43	1	7	13	7	7·26	33	12
11	55	M	239 (108·4)	56	7·38	47	−2	11	13	5	7·29	34	10
12	58	F	257 (116·5)	74	7·38	40	1	5	16	6	7·30	34	9
Mean values	35	—	222 (100·6)	62	7·37	40	1·25	7·8	16·3	7	7·29	32	10·5

blood-urea, and electrolyte values, and a normal renal ability to excrete an acid load.[1] The *p*H, P_{CO_2} and base deficit in arterialized capillary blood samples obtained before and on alternate days during fasting were estimated using the Micro-Astrup method.[2] During fasting a liberal water intake was allowed, but apart from one cupful of beef extract daily no other foodstuffs or supplements were given. Exercise was limited to moderate ambulation within the ward area.

The acid–base indices are summarized in the Table. All patients developed a primary metabolic acidosis (base deficit > 2·5 mEq/l.) with some degree of respiratory compensation ($P_{CO_2} \leqslant 35$ mm. Hg). A significant acidaemia ($pH \leqslant 7.30$) was detected in all but cases 1 and 2, and in case 5 the *p*H fell to 7.31 as early as the second day of fasting. Though weight loss and ketonuria persisted throughout the period of fasting, any marked improvement in the blood-gases following the development of metabolic acidosis could be traced subsequently to surreptitious eating by the patients.

Whereas the metabolic acidosis of starvation is probably largely due to ketone production by the liver, the possibility of impairment in the body's mechanisms of dealing with an acid load cannot be overlooked. Though our patients were able to excrete an exogenous acid load beforehand, abnormal tubular function arising during fasting may have contributed to their acidosis.[3]

Our findings show that in obese fasting patients metabolic acidosis may develop rapidly and become unexpectedly severe. Moreover, failure to develop acidosis, or its sudden improvement during starvation treatment, is good evidence that the fast has been broken despite continued weight loss, ketonuria, and denial by the patient. Since underlying renal or pulmonary disease could aggravate acidosis, it would seem advisable to assess renal tubular and pulmonary ventilatory functions before fasting is commenced, and to assess acid–base status during treatment. It is now generally believed that the treatment of obesity by total starvation is safe, yet some of our patients seemed to find nibbling even safer.—We are, etc.,

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Difficult Case of Gout

SIR,—Gout may be difficult to diagnose, and in the case reported below the presenting history was totally misleading.

A 60-year-old, overweight labourer was referred to the orthopaedic clinic with a five-month history of recurring swelling over the metacarpophalangeal joint of his right middle finger. Though the swelling was episodic, it never subsided completely. At the clinic he described pain and swelling over the joint, which was slightly swollen and tender. There was no history of specific injury, but he performed very heavy labouring, breaking boulders with a hammer. *X*-ray examination revealed a foreign body, probably metal, lying in the soft tissues between the heads of the second and third metacarpals. It was thought that his symptoms were due to chronic infection arising from this foreign body.

Exploration of the dorsum of the hand was performed under general anaesthesia. A bursa and degenerate tissue were found over the metacarpophalangeal joint of the middle finger, and these were excised. The foreign body could not be found, and it was thought inadvisable to extend the exploration in the presence of periarthritis. Hydrocortisone was injected locally, and the wound was closed. The resected tissue was examined by the pathologist, who reported that the tissue was densely fibrotic but contained a few synovial clefts. There were small zones of fibroelastic activity and occasional giant cells. There was no haemosiderin deposition or calcification, and examination under polarized light was negative. The appearances were those of non-specific chronic tenosynovitis.

On the fourth postoperative day he reported with severe pain in his hand. The area around the wound was red and hot, but there was no evidence of sepsis. A plaster supporting splint was applied with marked improvement in symptoms.

At this stage the possibility of gout was considered, and the serum uric acid was found to be 11.2 mg./100 ml. In the presence of a normal blood-urea this was indicative of acute gout. The diagnosis was confirmed by subsequent detailed biochemical studies. *X*-ray examination three months after exploration showed degenerative arthritic changes in the second and third metacarpophalangeal and interphalangeal joints. The metallic foreign body was again demonstrated. His condition improved with colchicine and probenecid, though his grip did not return to normal.

X-ray examination in this case was quite misleading. A metallic foreign body was found, with no sign of joint damage in the initial films. In retrospect, this is not surprising, for other authors have reported similar findings.[1 2] It may well be that repeated and unnoticed trauma influences the site of gouty arthritis.[3] The high-protein diet necessary for labourers is a further possible factor in precipitating attacks of gout in susceptible individuals.

Diagnosis is difficult when symptoms and signs are not typical. Initial investigations by radiology, biochemistry, and histology may all be negative in the early stages of gout.[3 4 2] Serial investigations in such cases should be performed, and only persistently normal results, together with a failure to respond to uricosuric agents, should be allowed to discredit the clinical diagnosis. In this context patients must be warned that self-medication with salicylates will prevent the beneficial effect of probenecid. Both are uricosuric, but they act as competitors, and as a result neither is as effective in the presence of the other.

I wish to thank Dr. I. A. Anderson and Dr. W. B. Davis for biochemical and pathological details, respectively, and Mr. T. H. Norton for permission to publish.

—I am, etc.,

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Paracetamol Overdose and Liver Damage

SIR,—Paracetamol is widely used as a mild analgesic, and the few reported side-effects suggest a high margin of safety when used in therapeutic doses. The finding of liver necrosis in rats,[1] was followed by two reports of fatal hepatic necrosis in inmates of a mental institution,[2] a third fatality being mentioned by Thomson and Prescott.[3]

Case 1.—A 46-year-old male was admitted two hours after ingesting 75 paracetamol tablets. He had not received other medication and there was no history of liver or kidney disease. He was in good general condition, conscious, and apyrexial. The pulse was 80, and the blood pressure 130/90. There was no icterus, and the liver was not enlarged or tender. Gastric lavage was carried out without detectable product, and a diuresis was initiated with frusemide 40 mg. and 5% glucose by intravenous infusion.

On the second day he complained of right upper abdominal pain and vomited altered blood. He was icteric, and the urine output had fallen. The blood pressure varied from 120/70 to

TABLE I.—*Case 2. Investigations*

	Day 1	Day 2	Day 3	Day 4	Day 6	Day 8	Day 10	Day 18
Haemoglobin (g./100 ml.) ..	16·2			14·6			13·9	14·6
W.B.C./c.mm.	6,600			7,200			9,400	7,400
E.S.R.	2			2			6	6
Bilirubin (mg./100 ml.)		3·2	3·5	3·2	2·8	1·6	1·3	0·8
Alk. Phos. (K. A. units)		5·5	8·0	8·0	8·5	8·0	8·0	5·5
Thymol turbidity		0·5	1·0	1·0	1·0	1·8	4·5	0·8
S.G.O.T. (units/ml.)		840	2,000+	2,000+	168	129	70	20
Prothrombin activity (% average normal)		30	26	12	40	56	56	56

130/90. The urine contained 0.24 g./100 ml. protein, and the deposit showed a few leucocytes and large numbers of red cells. Platelets were 35,000/cu. mm., plasma urea 137 mEq/l.; bilirubin 5.5 mg./100 ml.; alkaline phosphatase 17 K.A. units; thymol turbidity 1.8. The plasma *p*-aminophenol level was not estimated.

On the third day he was drowsy and confused with facial oedema and conjunctival haemorrhages. The blood pressure fell terminally, being briefly maintained by the use of mephentermine, and the patient died of pulmonary oedema 80 hours after ingesting the tablets.

Case 2.—A 37-year-old male ingested 50 paracetamol tablets together with 200 mg. amylobarbitone sodium and a tot of whisky. He was admitted eight hours later and refused gastric lavage. He had received no other drugs. There was a confirmed history of drinking bouts but none of liver or kidney disease.

He appeared well and apyrexial. The pulse was 90 and the blood pressure 145/90. There was no icterus, and the liver was not enlarged or tender. A diuresis was instituted using frusemide 40 mg. and 10% mannitol by intravenous infusion. A mean diuresis of 450 ml./hour was sustained for 60 hours.

Three hours after admission he complained of upper abdominal pain and vomited altered blood. On the second day he was icteric and drowsy. The liver was not enlarged, but there was excess urobilinogen in the urine. The patient complained of persistent epigastric discomfort and extreme lassitude, but these remitted progressively. He was mobilized on day 12 and discharged the 18th day after ingesting the tablets.

The plasma urea rose abruptly on the fourth day to 77 mg./100 ml., but otherwise the urea and electrolyte values were within the normal range throughout. The results of investigations are given in the Table.

This patient was reassessed four months later, at which time he was well. All liver function tests were repeated and showed only a lowered prothrombin activity at 56% of average normal. Bromsulphalein retention and liver biopsy were normal. Intravenous pyelography and glucose tolerance curve were performed with normal results.

Post-mortem Findings.—Case 1: The lungs displayed marked pulmonary oedema. The liver was congested, and it contained multiple areas of yellowish tissue which, on section, showed acute centrilobular necrosis extending through the mid zone. There was no evidence of a cholestatic lesion. The kidneys were soft, with pale, swollen cortices. Sections showed tubule degeneration seen maximally in the proximal convoluted tubules. There was some cast formation also seen in the collecting tubules. The features seen represent acute tubular necrosis associated with massive liver necrosis.

The necropsy findings are similar to those recorded by Davidson and Eastham.[2] Other than the small amount of alcohol taken by the survivor, neither case described here had received drugs known to have hepatotoxic effects. A direct toxic effect of paracetamol on the liver is inferred.

Prescott[4] records significant increases in human tubule cell excretion rates following paracetamol ingestion, and the rat experiments of Boyd and Bereczky[1] also revealed acute toxic effects on the tubules. A direct toxic effect of paracetamol on the renal tubules cannot be dismissed.

The clinical features of both cases during the first 48 hours are very similar. The danger of liver damage occurring after a symptom-free interval following self-poisoning with paracetamol requires that observation be maintained for at least this length of time. The development of upper abdominal pain without pyrexia should be regarded with suspicion. Limited experience suggests that a diuresis induced by intravenous infusion is more hazardous in paracetamol poisoning, since acute tubular necrosis may occur without preceding hypotension (Case 1).

I wish to thank Dr. F. I. Lee and Dr. I. Weinbren for permission to publish the details of these cases. Dr. S. M. Murray kindly assisted with detailed reports on the pathological material of Case 1.

—I am, etc.,

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Another Side-effect of the "Pill"?

SIR,—Dr. D. N. Barber (9 November, p. 390) refers to his earliest report[1] of the effect of an oral contraceptive on tissues supporting the teeth, and relates this action to the relaxation of the pelvic joints during pregnancy. In this connexion I wish to report an instance in which there appeared to be suggestive evidence of association of a drug of this sort with a very unusual type of ligament relaxation.

The patient, a 31-year-old lady, came with the complaint that when she sat up, or turned over in bed, or sneezed she could both feel and hear something "cracking in the upper part of the front of my chest." Moderate, localized, momentary pain was said to be associated with this sensation. Both physical and x-ray examinations revealed no pertinent findings other than considerable tenderness with crepitation and abnormal mobility at the junction of the manubrium with the body of the sternum—that is, a subluxation at this site.

The patient stated that she had been a regular user of the contraceptive pill during the past 18 months, but that the symptoms of which she complained had been present for only about two months. She was ordered to discontinue use of the pill but to make no other alterations in her way of life. Now, after about seven weeks, she is symptom-free and will soon be returned to contraceptive medication to determine whether subluxation will reappear.

The relaxation of the pelvic joints that occurs during normal human pregnancy is alleged to be associated with appearance in the blood stream of a polypeptide hormone, relaxin, secreted by the corpus luteum. This relaxin, however, has no associated oestrogenic or progestational actions, which therefore leaves us without explanation for whatever ligament-relaxing action the pill may be found to have.—I am, etc.,

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Coronary Disease and Personality

SIR,—Your leading article on coronary disease and competitiveness (January 4, p. 1) interested me very much. It shows that the psychosomatic aspect of coronary disease is still considered worthy of a large scale investigation. There must be a physical link between the "coronary personality," distinguished by great ambition, compulsive striving, and a drive for recognition, and the coronary arteries, and this link through the mediation of catecholamines may be hypertension.

Established hypertension is often found in patients who develop coronary thrombosis and is accepted as a predisposing cause. Labile hypertension may not be considered, as the basal blood pressure may give a misleading impression of normality. Nervous strain, anxiety and tension, fear, and repressed aggression will often produce quite marked hypertension, which will subside once the offending strain is removed. Modern, civilized, competitive existence with its overcrowding, persistent noise, constant mental stimulation and aggravation, traffic conditions, television viewing of violence, and of exciting political and sporting events, will all contribute to this considerable variation of blood pressure, which in some patients will remain permanently raised. It has been suggested that this latter tendency is due to high resting cardiac output and a normal peripheral resistance progressing to the more usual situation of a raised peripheral resistance and a cardiac output in the normal range. The idea that exercise protects from myocardial infarction was suggested by the work done by Morris and others on London bus drivers and conductors.[1] However, the greater incidence of sudden deaths and myocardial infarction in bus drivers could have been mediated through a labile hypertension produced by driving constantly in heavy London traffic.

Fluctuating hypertensive filling of the atherosclerotic coronary vessels in a usually normotensive or hypertensive person may cause the trauma to the arterial wall which sets off changes leading to thrombus formation. This mechanical intimal injury may lead to intramural or intimal haemorrhage with rupture into the lumen, the break in the artery then being the site of the thrombus formation, and increased coagulability of the blood being an additional factor; or the artery may become occluded by an intramural haematoma. This may occur particularly if there is an inherited inferiority of the vascular structure. Mechanical intimal injury may also be considered as a primary change which predisposes to the depositioning of lipids, the rate and extent of