TABLE VII.—*Ovarian Tumours—Activity by Endometrial Response*

Tumours	No. of Tumours	Endometrium Examined	Active Endometrium	Active Endometrium and C.I. of 5+	Post-menopausal Bleeding		
					History of	And Active Endometrium	And C.I. of 5+
Serous cyst-adenoma	18	15	6 (40%)	5	8	4	5
Pseudo-mucinous cyst ..	19	16	6 (37·5%)	2	5	3	3
Adeno-carcinoma	33	15	6 (40%)	4	7	1	2
Feminizing tumour	5	4	3 (75%)	1	5	2	3
Masculiniz-ing tumour	1	1	1 (100%)				
Neutral tumour	4	3	1 (25%)	1			
Total	80	54	23 (42·6%)	13	25 (31·2%)	10	13

Discussion

Evidence has been presented that normal post-menopausal women secrete oestrogen in low quantities, but probably not from the ovary. The C.I. is 4 or below in 75% of these women, and evidence presented suggests that the endometrium is inactive in 99% of normal post-menopausal women.

In our series of 80 ovarian tumours found in post-menopausal women we found evidence of increased oestrogen production in over half of these cases, as measured by the C.I. In the 54 cases where endometrium was available, active proliferation or cystic hyperplasia was present in 40%. This contrasts markedly with Greene's series of slightly more than 1% endometrial activity in normal post-menopausal women.

Post-menopausal bleeding occurred in over 30% of our cases with ovarian tumour, and suggests that some hormonal effect may have been present.

It is suggested that the oestrogen in these tumours is derived from cells of the granulosa-theca type which persist in the post-menopausal ovary or develop with the growth of the tumour. It might be that these tumours develop from ovaries which, though macroscopically normal, produce elevated levels of oestrogen before progressing to tumour formation.

These ovaries would probably be found among those apparently normal post-menopausal women with elevated C.I.s.

It appears that of the three major types of ovarian tumour in this series the serous cystadenomas produce oestrogen more commonly than any other.

Unfortunately, biochemical methods of oestrogen estimation were not available for this study. Prospective studies of ovarian tumours from post-menopausal patients should include direct measurement of oestrogen levels.

Summary

A review of the literature on oestrogen production in post-menopausal women is presented, and evidence suggests that normally the ovary ceases functioning after the menopause, and that the low levels of oestrogen found are derived from some other organ, probably the adrenal.

A series of 80 consecutive ovarian tumours in post-menopausal women has been reviewed for evidence of oestrogen function, the presence of oestrogen being determined by the cornification index and/or endometrial activity.

Using the C.I. as an indicator of oestrogenic function, it appears that increased levels of oestrogen are found twice as commonly in post-menopausal women with an ovarian tumour as in normal post-menopausal women.

Ovarian tumours are associated with endometrial activity in 40% of cases subjected to histological examination, whereas in normal post-menopausal women endometrial activity is found in about 1% of cases.

Serous cystadenomas appear to have greater oestrogenic function than other types of the so-called non-feminizing ovarian tumours.

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IMIPRAMINE POISONING IN CHILDHOOD

BY

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Imipramine ("tofranil") is an iminodibenzyl derivative chemically related to the phenothiazine series which is widely used for the treatment of depression in adults. Its many potential side-effects have been extensively documented (Azima and Vispo, 1959; English, 1959; Foster and Lancaster, 1959; Fullerton and Boardman, 1959; Mann, Catterson, and Macpherson, 1959; Segal and Howarth, 1960; Curran and Barabas, 1961), and the dangerous and sometimes fatal consequences of overdosage are well recognized (Brooke and Weatherly, 1959; Lancaster and Foster, 1959; Levene and Lascelles, 1959; Manners, 1960; Lee, 1961). Nevertheless, it does not yet seem to be generally realized that in young children serious poisoning can be caused by relatively small doses of imipramine, or that the resulting clinical picture is remarkably characteristic, and in its fully developed form perhaps unique.

Case reports of childhood poisoning are few, and a search has revealed only three detailed descriptions (Arneson, 1961; Alajem and Albagli, 1962; Garrison and Moffitt, 1962), two short notes (Noack, 1960; Connelly and Venables, 1961), and the passing comment by Fruthaler and Snyder (1962) in a general review of childhood poisoning that their personal experience includes one fatal and one non-fatal case. Yet during one eight-month period in 1961–2 at least seven Birmingham children were accidentally poisoned with imipramine, one of them fatally, suggesting that this is in fact an important and increasingly

common paediatric hazard which should be further documented. The illnesses of five of these seven children are described below.

Case Histories

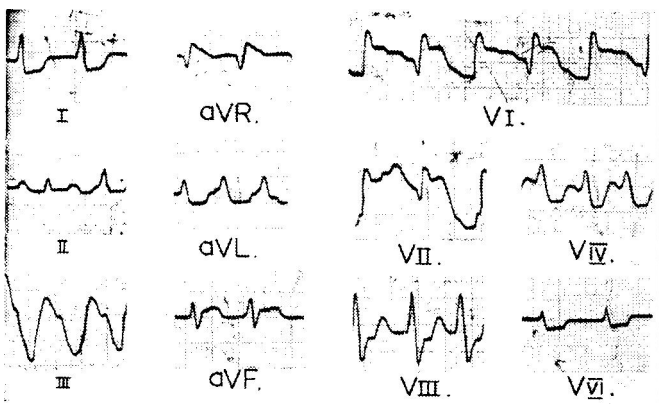
Case 1.—A boy aged 2 years 9 months ingested an uncertain quantity of imipramine. After six hours he was noticed to be staring and crying out in a strange manner. After a further 24 hours he vomited, became semiconscious, and was admitted to hospital. He had recurrent attacks of opisthotonos, rolling of his eyes, shaking of his arms, and raising of his extended legs in the air. His tendon reflexes were very brisk. Blood-pressure was 135/90 mm. Hg; no abnormal cardiovascular findings were recorded. He was sedated intermittently with paraldehyde; after 48 hours he was much improved, and after five or six days was apparently quite recovered.

Case 2.—A boy aged 1 year 7 months ingested 75 mg. of imipramine, vomited an hour and a quarter later, then became pale and increasingly drowsy. After four hours he was asleep but rousable, when he seemed disorientated. Pulse was 103 and regular; blood-pressure was recorded as "difficult to obtain, 130/? mm. Hg." He recovered spontaneously and completely within 24 hours.

Case 3.—A boy aged 5 years ingested not more than 75 mg. of imipramine and possibly some thioridazine ("melleril") tablets. Within an hour he became giddy and appeared to be unable to walk straight. After two hours he was semi-comatose, very restless when examined, and showed involuntary tonic contractions of muscles. Pulse was 150, blood-pressure 135/100. He recovered spontaneously and completely within 48 hours.

Case 4.—A boy aged 1 year 3 months ingested a maximum of 100 mg. of imipramine. After two hours he had a convulsion and was brought to hospital. Temperature was 102.2° F. (39° C.), there were almost continuous clonic movements of the entire body, the pupils were dilated and fixed, and there was a striking nystagmus. He was variably cyanosed; the radial pulse was thready, irregular, and uncountable; and the heart sounds were faint and irregular. The impression was of a desperately ill child in acute cardiovascular failure. Blood count showed 28,200 white cells per c.mm. (polymorphs 86%). Cerebrospinal fluid pressure was 260 mm. but the fluid was otherwise normal. He was given oxygen, pharyngeal toilet, and antibiotics; after two intramuscular injections of 2 ml. of paraldehyde 20 minutes apart he stopped convulsing, but his condition remained precarious for several hours, with a feeble and irregular pulse. He gradually improved thereafter, but was not fully conscious for 36 hours; he remained ataxic for a further two days, and was not really himself for 10 days. An electroencephalogram three weeks after the incident was normal.

Case 5.—A boy aged 1 year 6 months ingested 350 mg. of imipramine. A successful saline emetic was given by his parents almost immediately, but after one and a half hours he began shouting as if in pain. He was confused and excitable at first, but became gradually comatose; muscle tone was very variable, involuntary movements became more pronounced and ultimately developed into frank convulsions. His pulse became thready and irregular, particularly in regard to volume, and blood-pressure was unobtainable. The electrocardiogram (E.C.G.) was grossly abnormal (see Fig.), and is further commented upon below. Convulsions were controlled with intramuscular paraldehyde, and nine hours after ingesting the tablets he regained consciousness. After another three hours he suddenly had some further limb twitchings, collapsed, and died. Necropsy (Dr. K. W. Walton) revealed little of note. There were some pulmonary oedema and hypostatic congestion which were regarded as terminal changes of no specific significance, and diffuse cerebral oedema which was attributed to terminal anoxia. The myocardium was rather pale and flabby, but like the lungs and brain showed no significant histological changes.



Electrocardiogram from Case 5.

The Literature

The first report of imipramine poisoning in a child appears to have been that of Noack (1960). The patient was a boy of 2 years 6 months who consumed an estimated 2,500 mg. of imipramine. He developed continuous convulsions within half an hour, stopped breathing, and died after some 90 minutes in spite of artificial respiration and cardiac massage. Post-mortem examination showed no macroscopic abnormality.

Connelly and Venables (1961) described the case of a girl of 2 years who took between 375 and 500 mg. of imipramine. Convulsions developed within three hours, and she was noted also to have a persistent cardiac irregularity. Her E.C.G. showed a bizarre pattern, with deformity of the S–T segments and bursts of rapid beats in which the ventricular complexes were mostly quite abnormal and grossly widened. Sinus rhythm returned after 12 hours.

Arneson (1961) reported a near-fatal case of poisoning in a boy aged 1 year 7 months who was estimated to have ingested 1,500 mg. of imipramine and to have retained perhaps half of this after vomiting and lavage. He went into status epilepticus, was given intravenous amylobarbitone sodium, stopped breathing, and required artificial respiration for five hours. His pulse was feeble and irregular, and the E.C.G. showed total disruption of normal sinus rhythm, complete heart-block, ventricular beats originating from various foci, and extremely widened QRS complexes and depressed S–T segments, indicating a marked conduction defect within the cardiac musculature.

Garrison and Moffitt (1962) observed a boy of 1 year 10 months who ingested 500 mg. of imipramine. After an hour he became restless, screamed, waved his arms wildly, and went into extreme opisthotonos. After a further hour he was admitted to hospital in status epilepticus. His seizures were controlled by intravenous amylobarbitone sodium, but his respirations were shallow, gasping, and laboured, and he had twitching movements of the arms and legs. Systolic blood-pressure was 40 mm. Hg; the pulse was markedly irregular. His E.C.G. showed striking changes interpreted as ventricular flutter, paroxysmal atrial tachycardia, atrial fibrillation, and atrioventricular block. Treatment included intravenous fluids, hypertensive agents (which were ineffective), and artificial respiration for four hours. After 24 hours he was quite recovered.

Alajem and Albagli (1962) reported the case of a girl aged 1 year 6 months who ingested 375–500 mg. of imipramine and despite gastric lavage suddenly went into status epilepticus after one and a half hours. The pulse was irregular and feeble; the E.C.G. showed irregular ventricular activity, widened QRS complexes, and considerable S–T deviation and T-wave change. Recovery was eventually complete.

Discussion

The occurrence of striking E.C.G. changes is a notable feature in four of these reported cases, and to this group can now be added Case 5 of the present series. In the latter tracing (see Fig.) the dominant rhythm is a supraventricular tachycardia with ventricular complexes widened by conduction delay. There are runs of ventricular tachycardia and considerable variations in rate. There is S–T segment shift due to a large injury current which is pointing rightwards and anteriorly into the muscle mass of the septum. The curious appearance in leads V1 and V2 seems to be due to an alteration in the magnitude of the depolarization forces—that is, "T wave alternans."

Although unfortunately no E.C.G. was taken in Case 4, the clinical signs in the cardiovascular system were identical with those found in the five cases whose E.C.G.s were obtained, and a similar lesion was presumably present.

The pharmacological basis for the cardiovascular disturbances was investigated by Cairncross and Gershon (1962). In experimental animals imipramine caused tachycardia attributable to an anticholinergic block of vagal endings in the heart. With larger doses extrasystoles appeared and the E.C.G. showed broadening of the QRS complex, S–T segment depression, and abnormal T waves; these changes appeared also to be caused by a direct effect of imipramine on the heart. The same effects can be induced by smaller doses of imipramine if the animal is rendered hypertensive, one implication of this for the human subject being that any extra cardiac load may potentiate the cardiotoxic effects of imipramine. This obviously further underlines the necessity for prompt and complete relief of convulsions in the treatment of poisoning.

While the number of reported cases of imipramine poisoning in children is still small, certain features appear to be reasonably well established. Firstly, it is a dangerous drug for children. As little as 75–100 mg. (3–4 tablets) can produce severe symptoms in small children, and as little as 350 mg. (14 tablets) can prove fatal to a child of $1\frac{1}{2}$ years. Secondly, the clinical picture is so characteristic as to be virtually diagnostic (indeed, Case 5 of the present series was diagnosed correctly on clinical grounds although, misled by a filing error, the referring doctor had initially denied on direct questioning that imipramine had ever been prescribed for any member of the child's family). The central nervous system and the heart are principally involved. Consciousness is increasingly impaired; ataxia, nystagmus, and bizarre disturbances of muscle tone can be observed; convulsions and status epilepticus may supervene. In the more severe cases the cardiovascular system is strikingly affected. The pulse becomes thready and irregular, the heart sounds are disorganized, and the blood-pressure is variably diminished (although in milder cases raised blood-pressure levels seem sometimes to be recorded). Unusual and dramatic changes are found in the E.C.G., suggesting myocardial damage with gross defects of intracardiac conduction. There is considerable risk of cardiac arrest, and as in Case 5, this may remain even when the central nervous system has substantially recovered.

Apart from gastric lavage, treatment must obviously include control of convulsions, administration of oxygen, and preservation of a clear airway. E.C.G. studies would seem indicated in all but the mildest cases. The crucial problems are the maintenance of respiration and circulation, and, since if the period of acute poisoning be survived complete recovery is the rule, in seriously affected cases every possible therapeutic technique should be considered. Arneson (1961) felt that immediate intubation and continued artificial respiration (for five hours) were undoubtedly life-saving in her patient; Garrison and Moffitt's (1962) patient was given artificial respiration for four hours. The survivor of Fruthaler and Snyder's (1962) cases received artificial respiration and open cardiac massage. Another conceivable approach might be by the insertion into the heart of an artificial pacemaker incorporated in the end of a cardiac catheter. It is certainly clear that, if circumstances allow, these children are best treated where anaesthetic or other staff skilled in resuscitation are available, and, ideally, where facilities for cardiac surgery are also to hand.

Summary

Five cases are reported of imipramine poisoning in young children, one of which was fatal, and attention is drawn to the increasing importance of this hazard. The clinical picture is characteristic, being dominated by central nervous system manifestations, and in the more severe instances by cardiac disturbances with profound abnormalities in the E.C.G.

Cases 1, 2, and 3 were treated at Birmingham Children's Hospital, and I am grateful to Professor D. V. Hubble, Dr. W. C. Smallwood, and Dr. B. D. Bower for kindly permitting me to include their patients in the report. I am also indebted to Dr. P. M. Stock for interpreting the electrocardiograph of Case 5; to Dr. G. G. Gillam for much help and advice on the cardiological aspects in general; to Dr. K. W. Walton for his report on the necropsy findings in Case 5; and to H.M. Coroner for permission to refer to these findings.

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The report for 1962 of Birmingham University's Institute of Child Health states that it has continued its monthly meetings for school health medical officers and the medical officers of the Maternity and Child Welfare Department. The programme of these meetings has now been entirely recast and it has started a monthly postgraduate meeting for medical officers with selected subjects and speakers. It has extended the invitation to attend these lectures to medical officers of the Health Departments in neighbouring boroughs and counties. The meetings have been very successful, and the Department thinks that they will continue to be an important postgraduate activity for the medical officers of the School Health and Maternity and Child Welfare Departments, both in Birmingham and outside the city.