that its properties made it highly suitable for out-patient anaesthesia (Weese and Koss, 1954; Nobes, 1955a, 1955b; Ruddell, 1955; McColl, 1955; Young, 1956; Henderson and Mackett, 1957). On the other hand, its brevity of action (compared with thiopentone) has been disputed by some workers, who have also reported unfavourable side-effects and sequelae (O'Mullane, 1957; Simmons and Blanshard, 1957; Henderson and Mackett, 1958).

An earlier comparison between buthalitone and thiopentone (Simmons and Blanshard, 1957) showed no significant difference between them; the criteria of recovery were the patient's ability to obey verbal commands and to rise unaided to the sitting position. But such a method hardly measures *complete* recovery to normal consciousness. Various ways of doing this have been tried, such as the flicker-fusion frequency of a light source (Nilsson, 1953), and have proved impracticable.

The present method was conceived as a form of intelligence test which might be suitable for use in a busy out-patient department. We have shown that it is in fact practicable and that it combines simplicity with objectivity. It is suitable for almost all patients, making no great demands on their co-operation and inducing no fatigue. Should the experiment be repeated it would probably be wise to specify exact times at which the tests should be made. This would simplify the analysis and obviate the risk of a subjective judgment being used to determine when the first test should be given.

Summary and Conclusion

A new method is described of comparing the rate of recovery from barbiturate anaesthesia. The method is simple and assesses recovery to very near normal consciousness. This method was used in a small trial, and there was found to be no statistically significant difference between buthalitone sodium and thiopentone sodium; it is unlikely, therefore, that there is any great advantage, in respect of rate of recovery, to be gained by using buthalitone rather than the well-established thiopentone.

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"In connexion with forms being prepared by the National Road Safety Council for the reporting of traffic accidents, the Public Health Committee recommended that provision be made on these forms for the recording of information whether the driver at the time of the accident was likely to be under the influence of any therapeutic substance the nature of which should also be specified. This recommendation was made in view of the widespread habit of self-medication and the hazards associated with the use of certain tranquillizing and other drugs freely used by the public." (*Health*, Journal of the Commonwealth Department of Health, Australia, September, 1959.)

LONG-TERM FOLLOW-UP OF 32 PATIENTS IRRADIATED FOR THYMIC ENLARGEMENT IN INFANCY

BY

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Irradiation of the thymus gland in infancy was often practised in the thirties for the treatment of a variety of symptoms thought to be associated with thymic enlargement. Prominent among these symptoms were stridor and attacks of cyanosis, dyspnoea, and syncope. X-ray or radium therapy was often employed in such cases, even when radiological evidence for enlargement of the thymus was uncertain. In America, "prophylactic" irradiation was even given to symptom-free infants shortly after birth at one time (Conti and Patton, 1948).

Thymic irradiation went out of fashion in many centres after about 15 years, when it had become apparent that the symptoms ascribed to enlargement of the gland usually cleared as quickly without irradiation. This was fortunate, as it was not realized until some years later that there might be an association between such treatment and the development of thyroid cancer and leukaemia.

Attempts to assess the degree of correlation have been made either by investigating the radiation histories of patients who developed thyroid cancer and leukaemia in childhood (Duffy and Fitzgerald, 1950; Clark, 1955; Stewart *et al.*, 1958; Polhemus and Koch, 1959; and others) or, as in a notable series reported by Simpson *et al.* (1955), by tracing children who had received thymic irradiation in infancy.

In view of the findings an attempt was made to follow up infants who had received irradiation for thymic enlargement at the Middlesex Hospital and at the Hospital for Sick Children, Great Ormond Street. While it is recognized that statistically valid conclusions must be based on larger numbers, this follow-up is presented for its interest and in the hope that it will be possible to combine results from other centres.

It is probable that the subsequent history of such patients sheds little light on the effects of thymic enlargement *per se*, as it is now recognized that true enlargement occurs rarely, and that the thymuses commonly reported as enlarged were probably normal.

A total of 32 infants were found to have received thymic irradiation by deep x rays or radium between 1932 and 1950. In all, 27 patients have been traced to the present time and are alive: one has been traced to 1946, and three have died. Only one has remained untraced since treatment was given and has not been notified as having died.

Sex.—Of 31 infants traced, 20 were male. This preponderance of male infants has been observed previously.

Age at which irradiated (Table I).—Of the traced patients, 16 had been treated at the age of 3 months or less. The age at irradiation may well be important, as it will influence the percentage area of body surface irradiated and as there may be an increased sensitivity to radiation at this time.

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Follow-up years after irradiation (Table II).—All but one of the patients had been irradiated more than 10 years ago and 14 more than 20 years. The number of patient-years in the follow-up totals 566. This may be compared with the incidence of leukaemia following irradiation of the thymus as calculated by Polhemus and Koch (1959)—that is, approximately 1/3,300/year. It also appears that a latent period of the order of five to eight years might be expected. The inclusion of follow-up years after the expiry of this period might therefore tend to reduce the apparent incidence of this complication. Similar considerations apply to cancer of the thyroid following thymic irradiation in infancy, but here the latent period ranged from 6 to 24 years in 16 cases reported by Simpson and Hempelmann (1957), and from 5 to 37 years in nine cases reported by Wilson *et al.* (1958).

Dose of Irradiation.—The figures for this were either obtained from contemporary notes or calculated in retrospect from available data. The accuracy of the figures quoted can only be approximate in many cases. The dosage of deep x rays directed at the upper mediastinum was stated to be 1,540 r in one case, 1,400 r in one case, 600–900 r in eight cases, and 180–450 r in six cases. The remainder were treated by application for 16 hours of a “radium bib” (Moncrieff, 1938), equivalent to approximately 740 r, assuming a constant distance of 1 cm. from the skin, or by radium applications ranging from 640 mg.-hours as in the “bib” to 1,800 mg.-hours, with other details unspecified.

The rate of irradiation ranged from 800 r in 6½ hours to 180 r in 9 days.

The *presenting symptoms* on referral are set out in Table III.

Subsequent Course.—Three patients were found to have died. One, a mongol, was treated with a “total skin dose 26 r [sic]” at 2–3 months, but died 14 days later with persistent vomiting. The second infant received radium treatment to the upper mediastinum at the age of 7 weeks and was subsequently treated with thyroid tablets until she died suddenly at the age of 5 years. At 18 months it had become evident that she was mentally retarded. She did not appear to benefit from the thyroid therapy, so it is an open question whether

her thyroid might have been damaged by the irradiation. The third death occurred at the age of 26 in a motor accident. The post-mortem report mentioned nothing relevant to this investigation.

Associated Abnormal Conditions

Table IV summarizes the associated abnormal conditions found among the 28 surviving patients.

One patient developed a nodular goitre 22 years after irradiation from a radium “bib” at the age of 3 months. (Simpson and Hempelmann (1957) found eight cases of

TABLE IV.—*Abnormalities and Illnesses Diagnosed, in Relation to Time of Irradiation*

Case	Illness	Onset after Irradiation	Age at Onset
1	Mongol	—	Birth
	Diarrhoea and vomiting	2 weeks	2½ months
	Died	3	—
2	“Violent catarrh”	“Soon”	c. 3 months
	Failure to thrive; continuous treatment with thyroid tablets	—	?
	Mental defect	16 months	18 months
	Died suddenly	5½ years	5½ years
3	Nodular thyroid goitre	13	13
	Abnormality of cervical vertebrae	—	(congenital)
4	Slight diffuse thyroid enlargement	16	17
5	? Growth retardation (but final stature normal)	5	5
6	Neurilemmoma in sternomastoid	5	5
7	Pulmonary tuberculosis	21	22
8	Bronchiectasis; lobectomy	15	15
9	“Chesty”	?	?
10	“ ”	11 years	11 years
11	“ ”	?	?
12	“ ”	?	“Till age of 14”
13	Asthma	13 years	13 years
14	Pneumonia	3	3
15	Diarrhoea and vomiting for 3 weeks*	3 days	3 months
16	Diarrhoea	1 month	9
17	Cerebral palsy; mental defect	—	“From birth”
18	“Highly strung”	5 years	5 years
19	Grand mal	11	13
20	? “ ”	—	2 months

* It is possible that the diarrhoea and vomiting were a direct sequel to the radiation given.

thyroid “adenoma” among 1,400 patients previously irradiated for thymic enlargement, and only one in their control series.) No histological report of this goitre is available. A further patient had a *slight diffuse enlargement of the thyroid* when seen 16 years after irradiation, aged 17. The *neurilemmoma* discovered in another patient was first noticed at the age of 5, situated in the upper part of the right sternomastoid and removed at the age of 14. *Abnormalities of cervical vertebrae C 2–6* were found in the patient with the nodular goitre. The vertebral bodies of C 5 and 6 were hypoplastic and fused; there was also some deformity of the articular processes and laminae of C 2 and 3, and an abnormal spur of bone extending downwards from the fourth cervical spine. Radiation exposure can modify vertebral growth (Neuhauser *et al.*, 1952) and may be responsible for the development of exostoses, but the present abnormality was more probably congenital.

The number of *respiratory illnesses* may be related to the high incidence of respiratory symptoms presenting at the time of irradiation in infancy. No effect on *growth* could be detected, though one male of 5 ft. 6 in. (168 cm.) at the age of 23 years was suspected of growth retardation at the age of 5. There were no cases of *leukaemia*, but the chance of encountering one in such a limited series is small. It may be that most of the patients reviewed here have passed the danger period for the consequential development of thyroid cancer or leukaemia, but larger numbers of cases will have to be

TABLE I.—*Age at Which Irradiated*

Age in Months:	0–1	2–3	4–6	7–12	13+
Traced	2	12	5	6	3
Died	—	2	—	—	1

TABLE II.—*Follow-up Years After Irradiation*

Years:	0–5	6–10	11–15	16–20	21–25	26–30
Traced	—	1	5*	9	9	4
Died	2	—	—	—	1	—

* One patient was followed up 11 years in 1946.

TABLE III.—*Indications for Treatment*

Laryngeal stridor	21
X-ray evidence*	31
Cough and dyspnoea	11
Syncope, “blue” or “white” attacks (excluding frank grand mal)	9
Other causes†	8

* Cases included under this heading were reported as having abnormal mediastinal shadows, thought to be due to thymic enlargement. Where this was queried in the report the case has nevertheless been included. Most of the films are no longer available.

† Other causes comprised: dilated upper abdominal veins (1), head held askew (2), nose-bleeds (1), breath-holding attacks (1), fits (3).

collected before any definite statement can be made concerning the risk throughout the subsequent life of these patients.

Summary

Thirty-two patients who received irradiation for suspected thymic enlargement in infancy between 1932 and 1950 are reviewed. Thirty-one of these have been traced. Three have died, one possibly from the acute effects of the radiation. One case developed a nodular goitre 22 years after the irradiation, another had slight diffuse enlargement of the thyroid at the age of 17, and another had a neurilemmoma removed from the neck at the age of 14. There were no cases of leukaemia.

I thank Professor Alan Moncrieff, on whose suggestion this work was undertaken; Dr. E. W. Hart for allowing me access to the records of patients he followed up in 1946; Dr. M. Lawrence, latterly of the Hospital for Sick Children, Great Ormond Street, and the Cancer Registration Section of the Registrar-General's Office, Somerset House, for assistance in tracing the patients. An abstract of this paper was read at the Royal Society of Medicine in May, 1959.

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Kadatz (1957) showed that a dose of 152.4 mg./kg. was capable of eliminating the pain reaction in 50% of a group of 30 mice. This compares with a comparable dose of acetylsalicylic acid of nearly 300 mg./kg. It was also shown to possess antipyretic and anti-inflammatory activity.

The LD₅₀ for rats was shown to be 0.73 g./kg. by intraperitoneal injection and 10 g./kg. by mouth. Toxic doses produce central depression with respiratory failure. High individual doses of 3 g. by mouth were given to dogs without ill effect (weight of animals 9–14 kg.). The long-term toxicity studies on dogs showed no harmful effects after six months on a dose of 0.2 g./kg. daily by mouth. The treated animals remained normal as regards growth and behaviour, and their blood picture, coagulation time, and prothrombin time were normal at the end of the test period.

In the rat a dose of 100 mg./kg. was completely absorbed after 15 hours and none appeared in the faeces. In man 75% of an oral dose appears as metabolites in the urine within 33 hours and complete excretion takes at least 40 hours. By comparison, 4 g. of salicylic acid is completely excreted in the urine within 15 hours.

The metabolites of chlorthenoxazin (B.P.) have been studied by means of paper chromatography and can be estimated quantitatively after acid hydrolysis in the form of total salicylates and total gentisate. Estimations of serum levels in human subjects showed a maximum seven hours after administration. This compares with a maximum serum level of acetylsalicylic acid three hours after ingestion, suggesting that chlorthenoxazin is absorbed and excreted more slowly than aspirin and that it tends to accumulate within the body after repeated dosage, giving a higher serum level after some days' administration.

The problem of the assessment of the analgesic activity in man was approached initially by means of small-scale double-blind trials in patients suffering constant pain from osteoarthritis (D. W. and P. H. K.). Compound codeine tablets and aspirin were used as controls, and the results showed that the effect of the two substances, measured by the subjective response of the patients, did not differ significantly. It was confirmed that chlorthenoxazin has a period of action up to 50% longer than aspirin or compound codeine tablets; there were no noticeable side-effects. One of us (P. H. K.) used chlorthenoxazin in an experimental study on pain induced in volunteers by injecting 6% saline into the interspinous ligament. Statistical analysis of the results revealed an analgesic action equivalent to paracetamol.

A further controlled trial was carried out with "valtorin" (compound tablet containing 250 mg. of chlorthenoxazin and 200 mg. of phenacetin) on 1,000 patients following dental extraction (P. M. P.). The analgesic effect of the compound was equivalent to that obtained with compound codeine tablets.

Preliminary experience in these trials suggests that chlorthenoxazin is relatively free from gastro-intestinal irritant action. Seven subjects, six of whom were known aspirin "bleeders," showed no evidence of occult blood in the stools after administration of 1,800 mg. daily (the average therapeutic daily dose).

Experience with the long-term use of the drug, which extends in a few cases to as long as 18 months, has revealed no diminution in haemoglobin levels.

Preliminary Communications

Chlorthenoxazin — A New Analgesic

During 1957 136 suicides were attributed to overdose of aspirin and 41 further accidental deaths resulted from its use. An increasing number of authors refer to the hazards resulting from persistent haemorrhage into the gastro-intestinal tract which is frequently associated with aspirin therapy. In the face of this disadvantage one must assume that the continued use of aspirin as the standard mild analgesic is due to the lack of an acceptable alternative.

Biochemical research during the past decade has been extensively concerned with compounds of the benz-methoxane series, and in 1951 the substance 2-(β -chloroethyl 1)-2,3-dihydro-4-oxo-(benzo-1-3 oxazin) was submitted to pharmacological investigation.

To establish its analgesic action, pilot testing of mice by the tail-tip method of Haffner (1929) was followed by extensive experiments using the hot-plate method of Chen and Beckman (1951). By the latter method