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-chlorethyl 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

Work with the drug is continuing, and, if our present results are confirmed, chlorthenoxazin should prove a most useful addition to the present range of mild analgesics.

We are grateful to Messrs. C. H. Boehringer Sohn, Ingelheim am Rhein, for supplies of chlorthenoxazin and valtorin.

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Practical Experience with the Peak Flow Meter

Many elaborate instruments are available for measuring expiratory flow rates, but few are suitable for use in the consulting-room, in the factory, or at the patient's own bedside. The peak flow meter whose workings were described by Wright and McKerrow (1959) has been used by us both in clinical practice and in epidemiological surveys, and has proved itself to be a practical aid in the investigation of chest conditions.

RESULTS IN NORMAL PERSONS

The mean reading for 105 males was 53.7 (equivalent to 537 litres per minute) and for 74 females the reading was 38.0. These normal values were based upon 69 staff at Queen's College, Dundee, 30 staff at Ashludie Chest Hospital, and 80 symptom-free flax-workers.

In men the blowing power was found to decline 0.29 unit (S.E. 0.10) for each year's increase in age, and for every extra inch of height the blow increased by 1.44 units (S.E. 0.23). Weight had no significant effect, and the values for women did not change significantly with age, height, or weight.

The peak flow readings were compared with expiratory flow rates (3/4 second forced expiratory volumes) measured either on a spirometer of the type described by Bernstein, D'Silva, and Mendel (1952) or on the modified Gaensler (1951) apparatus. In order to mitigate the effect of age, sex, and body-build, it was found convenient to use the ratio of 40 times this volume—that is, the E.F.R. 40 of Kennedy (1953)—to the predicted value of the maximum breathing capacity (M.B.C.) of Needham, Rogan, and McDonald (1954).

COMPARISONS WITH OTHER INSTRUMENTS

During a survey in a flax factory and flax mill, measurements were obtained on both the peak flow meter and the Mendel spirometer for 65 subjects. For 41 men the coefficient of correlation between the two instruments was 0.81, and for 23 women 0.62. These can

be compared with the coefficient of 0.86 obtained by Higgins (1957). The mean values of various categories for the two instruments are shown in the Table.

Mean Values for the Two Instruments

	No.	Peak Flow Meter (As % of 60 for Men or 40 for Women)		Spirometer E.F.R. 40 Pred. M.B.C. × 100	
		Best of 3 (%)	Average (%)	Best of 3 (%)	Average (%)
Symptom-free ..	13	95	91	96	89
Byssinosis (alone) ..	9	89	84	91	99
Simple bronchitis ..	19	79	75	83	81
Complicated ..	5	73	69	78	74
Emphysema ..	4	36	35	36	34
Miscellaneous conditions* ..	15	74	71	82	79

* These include bronchospasm (9), upper respiratory catarrh (4), bronchiectasis (1), and hypertension (1).

The coefficient of variation (standard deviation/mean as a percentage) was approximately 30% for both instruments, whether the best or the average reading was used. This represents the variation between subjects. The variation between tests on the peak flow meter at different times in the same subject was 10%, and the variation between blows at the same test in the same subject was only 6%; this last was only one-half of the corresponding variation for the spirometer (11.5%).

RESPONSE TO BRONCHODILATOR DRUGS

Forty-five hospital patients with bronchospasm were tested with each of four drugs (subcutaneous adrenaline, intravenous aminophylline, and prednisolone and isoprenaline by insufflation) as a guide to maintenance therapy. Their improvement, shown on the Graphs, was estimated by measurements before and after the administration of the drugs, using both the peak flow meter (horizontal axis) and a Mendel or Gaensler spirometer (vertical axis). The patients have been divided into three categories in order to demonstrate the differences in response that may occur.

Those diagnosed as chronic asthma show the best correlation between the two measurements. Those in the asthmatic bronchitis group show less spectacular improvement and the scatter is wider. The correlation is least in the emphysema group, who show little response to the drugs used.

DISCUSSION

The only occasion when the peak flow meter failed to reproduce the results obtained with other spirometers

Response to bronchodilator drugs as measured by peak flow meter and by spirometer. Vertical axis represents change in spirometer readings after administration of drugs. Horizontal axis represents change in peak flow readings.