Brit. J. Psychiat. (1964), 110, 411–414

Comparison of Psycho-therapeutic and Anthelmintic Activities

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The need for the assessment of phenothiazines and other drugs used in mental conditions is increasing as new products are described. Testing these drugs on patients is cumbersome and time-consuming. It would be valuable if a preliminary test could be made on some animal in which the effect on the nervous system can be easily assessed.

When any new drug is introduced in human disease without preliminary animal trials the placebo effect is always extraordinarily large, and the magnitude of the errors which can be obtained has been demonstrated on many occasions, particularly by Wolff (1959). Probably more papers at the present time are being produced on tranquillizers than on any other subject, but it has been shown by Loranger, Prout and White (1961) that under 20 per cent. of these papers meet the minimum standard of scientific acceptability.

Monkeys, dogs, cats, rats, rabbits, fish and even spiders have been used in psychological experiments and most of these have also been utilized in trials of psychotropic agents including the phenothiazine drugs, but for obvious reasons none has proved entirely satisfactory.

The present work suggests another experimental approach to the problem which has the advantage of giving rapid and easily repeatable results.

The Phenothiazines

By far the largest number of drugs used in mental disease belong to the phenothiazine group. On examining the chemical structure of the more potent of these drugs, we were struck by the fact that the attachment of a piperazine grouping to the nucleus greatly increased the effectiveness of the drug and, at the same time, largely eliminated certain undesirable side-effects. We also noted that both the phenothiazine nucleus and the piperazine side chain were known powerful anthelmintics. The action of these has been shown to be on the primitive nervous system of the worm (Baldwin, 1943, 1948; Goodwin and Standen, 1954). In view of the suggestion that psychotic states may in some way be associated with impulses arising from abnormalities in the reticular system, and as chlorpromazine has been shown to have marked action on this site, we investigated the anthelmintic activity of some of the phenothiazine drugs used in psychiatry. The object was to discover if this activity was in any way paralleled by the potency of the drugs on psychotic patients.

Experimental Work

The testing of anthelmintic activity is always time-consuming and inaccurate, so it was decided to use only one method, that of Baldwin (1943). From a female *Ascaris lumbricoides* worm from a pig the anterior 2 cm. containing the ganglion nerve ring was removed. A cotton ligature was tied to the extreme rostral end and attached to a hook fixed at the bottom of a short test tube. A second ligature was applied to the caudal end of the segment, and this attached to a lever writing on a smoked drum.

Drugs to be tested were obtained in solution form and added to the Ringer solution in varying concentrations, and the average minimum effective concentration required to produce paralysis in the worm was obtained.

Results and Conclusions

Using thymol, naphthol and other common anthelmintics our results were similar to those

obtained by Baldwin (1943). The peculiar thing, however, noted in Baldwin's results was that the popular veterinary anthelmintic phenothiazine was found to have no effect. As we intended to work on phenothiazine preparations, this finding was of importance, and was probably explainable by the fact that phenothiazine is only 1 in 800,000 soluble in water. Any effect on worms is probably produced by chemical changes in the gut, changes which can lead to toxic absorption and the development of marked photosensitivity (Monning, 1947).

Using the better known phenothiazine psycho-pharmaceuticals the concentration of the drug required to produce reversible immobility in the *Ascaris* segments were as shown in the table below. This also includes a table showing a list of the comparative doses and therapeutic efficiency of many of the phenothiazines used in psychiatry. The tables have been composed from papers by Ayd (1961), Schiele (1962), Levy and Ban (1962), Cattell, and Malitz (1960) and Roberts (1961).

It will be noticed in this table there is a wide variation in the maximum dose of the drugs recommended as psycho-therapeutic agents. There is also considerable variation in the estimation of the potency of the drugs compared with chlorpromazine as a standard. The order of potency in all the reports works out at approximately the same.

Examination of the table shows considerable correlation between the psycho-therapeutic and anthelmintic activity. Those accepted as being clinically more effective at lower doses generally producing paralysis at greater dilutions. The relationship is not proportional, but shows the same trend.

When one considers the wide divergence of suggested dose and the crude methods for evaluation in the human species, it might well

TABLE

	Ayd (1961)		Schiele (1962)	Levy and Ban (1962)		Cattell and Malitz (1960)		Roberts (1961)	Anthelmintic Activity	Relative Anthelmintic Activity
	Dose mg.	Relative Potency	Relative Potency	Dose mg.	Relative Potency	Dose mg.	Relative Potency	Relative Potency		
1. Chlorpromazine (Largactil, Thorazine)	300– 800	1	1	150– 500	1	100–600	1	1	1: 1,000	1
2. Promazine (Sparine)	500–1,000	0·8	0·75	75–1,000	0·5	100–600	1	0·5	1: 500	0·5
3. Mepazine (Pacatal)	500–1,000	0·8	0·5	75– 400	1·2	75–150	4	—	1: 1,000	1
4. Triflupromazine (Vesprin)	100– 300	2·5	2	75– 300	1·7	30– 90	7	2	1: 1,000	1
5. Prochlorperazine (Compazine)	75– 100	8	4	15–1,000	0·5	14– 45	13	4	1: 3,000	3
6. Trifluperazine (Stelazine)	10– 60	13	10	2– 30	17	3– 15	40	10	1: 5,000	5
7. Perphenazine (Trilafon)	32– 64	12	6	6– 24	21	6– 48	12	5	1: 2,500	2·5
8. Fluphenazine (Permitil, Prolixin)	2– 10	80	20	1– 2	250	1– 10	60	60	1: 5,000	5
9. Thioproperazine (Majeptil)									1: 2,000	2
10. Chlorprothixine (Taractan)									1: 1,000	1
Non-Phenothiazine Tranquillizer										
11. Chlordiazepoxide (Librium)									1: 500	0·5
Anthelmintics										
12. Hexyl-Resorcinol									1: 2,000	2
13. B. Napthol									1: 2,000	2
14. Thymol									1: 1,000	1
15. Piperazine									1: 5,000+	5+
16. Mintic (I.C.I.) 2 (β Methyoxyethyl) pyridine Sulphate									1:10,000+	10+
17. Thiabendazole (Merck) (2-(4'-thiazolyl)-benzinidazole									1:10,000+	10+

be established that the relative potencies indicated by worm paralysis are in fact more realistic.

The results shown in the table indicate that this is probably an efficient method of evaluating this group of drugs, and we consider the work to be of some importance for the following reasons:

Firstly, it would appear that our work has shown that the *Ascaris* worm is probably a very useful, cheap and simple experimental animal for estimating the probable therapeutic activity of this group of drugs in human mental diseases. We consider that when a new drug is produced that is shown to be non-toxic to human beings, that the therapeutic dose could rapidly be calculated by comparison with the efficiency of other drugs on the *Ascaris* worm.

Secondly, it is probable that the primitive nervous system of the worm bears some pharmacological relationship to the reticular nervous system of the human being on which these drugs may well be acting.

Thirdly, it seems possible that other anthelmintics which could be proved by Baldwin's technique to act on the nervous system of *Ascaris lumbricoides* may prove of value in psychiatry. In a very limited number of suitable psychotic cases on which we have had the opportunity of trying the non-toxic drug piperazine in this hospital, we have been impressed with the results, though the number is not sufficient for us to come to any conclusion. It would be of interest, were the drugs found to be sufficiently non-toxic, to try the effect of the far more powerful anthelmintic "Mintic" of ICI, or Thiabendazole of Merck on suitable psychotics (Gordon, 1961).

A considerable amount of work on the chemical constitution in anthelmintic activity of phenothiazine and related substances has been done by Rogers, Craig and Warwick (1955), and they found there is no significant difference between the anthelmintic activity of phenothiazine and phenoxazine, but this latter substance has not been found effective in psychotic patients (Craig and Tate, 1962). Craig, Rogers and Warwick (1955) made further modifications in the phenothiazine ring, but have been unable to enhance the anthelmintic activity. In no case did they make the same substitutions that are now used in these psychopharmaceutical drugs.

Final examinations of our figures and those of previous workers shows that the toxicity of the phenothiazine drugs on the central nervous system and their maximum therapeutic dose are similar. The amounts required to produce excessive nervous irritability, restlessness and the Parkinsonian syndrome are only a little greater than that required to produce the desired tranquillization. The less potent of the drugs are most likely to produce photosensitivity, and this complication is noticed only rarely in the patients receiving the smaller doses of the more active drugs. Collier (1940), Craig and Warwick (1955) suggest that the toxic symptoms from phenothiazine are caused by oxidation products acting on the enzyme system. Craig, Tate, Donovan and Rogers (1960), have isolated oxidation breakdown products of the phenothiazine nucleus from calves suffering from photosensitivity. It is possible that the infrequency of photosensitivity in patients receiving the more potent drugs is probably due to the smaller doses of the phenothiazine nucleus.

Summary

A comparison between the anthelmintic and psychotopic activity of some phenothiazine and related drugs has been made. Some correlation is demonstrated. It is suggested that the motor cells of the primitive central nervous system of the worm may be related to the human reticular nervous system.

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