Reserpine exhumed

DAVID HEALY and MARIE SAVAGE

RESERPINE: ADVENT

Western medical attention was drawn to *Rauwolfia serpentina* by reports of its benefits in hypertension (Vakil, 1949). Reserpine was isolated from *Rauwolfia* and studies by Kline, Delay and others demonstrated that Indian claims that it had a place in the treatment of nervous disorders could be substantiated (Deniker, 1983). Its use in psychiatry grew. The comparability between its effects and those of chlorpromazine led Delay and colleagues to their classification of the neuroleptics as a group of drugs with diverse chemical structures but similar functional effects (Deniker, 1983).

RESERPINE: DEMISE

During 1954 and 1955, however, case reports appeared in the *Journal of the American Medical Association* (Achor *et al*, 1955; Muller *et al*, 1955; Schroeder & Mitchell-Perry, 1955; Kass & Brown, 1955), the *Lancet* (Wallace, 1955; Smirk & McQueen, 1955), the *New England Journal of Medicine* (Freis, 1954) and the *Annals of the New York Academy of Sciences* (Wilkins, 1954; Ferguson, 1955) to the effect that reserpine could make subjects depressed and suicidal. There were a number of further reports, especially from Canada (Genest *et al*, 1955; Lemieux *et al*, 1956) and Scandinavia (Faucett *et al*, 1957; Jensen, 1959).

In these reports, it was recorded that 10–15% of hypertensive subjects taking reserpine became depressed. From four to 30 cases of depression were reported in samples of 39–195 subjects, with one or two individuals attempting or completing suicide. This led to a comment in the *American Journal of Psychiatry* on the dangers of reserpine (Harris, 1957). Despite the efforts of a number of psychiatrists to counteract the 'hysteria' (Sarwer-Foner & Ogle, 1955; Ayd, 1958; Bernstein & Kaufman, 1960), reserpine entered mythology as a drug that was uniquely liable to provoke severe depressions that might culminate in precipitate suicide.

This view found its ultimate expression in the catecholamine hypothesis of depression, a central pillar of which was the 'accepted fact' that reserpine caused depression by lowering brain catecholamines. The dominance that this hypothesis achieved produced a vicious circle in that, if depression was 'known' to be associated with lowered brain amine levels, given that reserpine reliably reduces amine levels, it seemed inevitable that it would cause depressions. The use of reserpine fell dramatically.

RESERPINE: EXHUMED

There are reasons to be sceptical about the claim that reserpine causes depression, and a number of implications if the initial claims were wrong.

The claims of reserpine-induced depression came from physicians rather than from psychiatrists. Reserpine's defenders were psychiatrists (Sarwer-Foner & Ogle, 1955; Ayd, 1958; Bernstein & Kaufman, 1960). This point needs to be put in historical context. Some years later, when amitriptyline was released, Merck decided that general physicians were unlikely to be able to recognise depressive disorders and that an extensive educational campaign was needed (Healy, 1997). The claims, therefore, that reserpine had induced depression mady by physicians such as Wallace, based in Geelong, or Smirk and McQueen, from Otago, need to be interpreted with caution. It is clear that these subjects became in some way dysphoric and agitated but it is less clear that they became depressed. In the majority of cases reviewed by psychiatrists, the diagnosis of depression proper was rejected, or where the individual did appear to be depressed a prior history of depression was noted, making it difficult to interpret the role of reserpine in producing the final state (Ayd, 1958).

The dose of reserpine used was of the order of 0.5–4 mg, which exceeds by tenfold the currently recommended optimal hypotensive dose. Psychiatrists surveying reserpine's effects at this dose pointed to clear neuroleptic-induced syndromes of excess transquillisation, demotivation and parkinsonism. Ayd (1958) who reported on 70 'drug-induced depressions' noted the comparability of features across states, whether these were induced by chlorpromazine or reserpine. Similarly, Sarwer-Foner & Ogle (1955) outlined comparable 'depressive' or 'anxious' reactions to treatment with either chlorpromazine or reserpine.

Reserpine produced at least two different states. After 2–11 months of treatment, a state of excessive tranquillisation appeared, that usually cleared up with dosage reduction or treatment discontinuation (Freis, 1954; Wilkins, 1954; Kass & Brown, 1955; Schroeder & Mitchell-Perry, 1955; Achor *et al*, 1955; Muller *et al*, 1955; Genest *et al*, 1955; Sarwer-Foner & Ogle, 1955; Lemieux *et al*, 1956). Others noted that the state responded to treatment with stimulants (Ferguson, 1955; Ayd, 1958), so that even many general physicians concluded that reserpine had caused problems but not a depression proper.

But another state could appear within hours or days of treatment commencing. This was characterised as follows: "increased tenseness, restlessness, insomnia and a feeling of being very uncomfortable" (Achor *et al*, 1955), "the first few doses frequently made them anxious and apprehensive . . . they reported increased feelings of strangeness, verbalized by statements such as 'I don't feel like myself' . . . or 'I'm afraid of some of the unusual impulses that I have'" (Faucett *et al*, 1957). Sarwer-Foner & Ogle (1955) describe the case of a subject who on the first day of treatment reacted with marked anxiety and weeping and on the second day "felt so terrible with such marked panic at night that the medication was cancelled". Such reactions were interpreted by some as evidence in favour of the then current theory that subjects with essential hypertension had a suppressed rage close to the surface (Faucett *et al*, 1957). A description by Ayd (1958), however, seems to point to something else: "they had motor restlessness

https://doi.org/10.1192/bjp.172.5.376 Published online by Cambridge University Press

which made their muscles taut, compelled them to pace the floor and did not permit them to sit without moving their legs".

Again these observations need to be put in context. Dyskinetic reactions were observed through 1954 to 1957, but even as late as 1957 experienced psychiatrists were liable to interpret them as 'hysterical' (Deniker, 1983). The first awareness that neuroleptics, and in particular reserpine, might cause akathisia appeared at the end of 1954 and the first proposal to use the term akathisia to refer to drug-induced tense restlessness was made in 1955 by Haase who "applied this term to the . . . symptom group, which we observed to be predominantly a result of higher dosages and particularly of reserpine" (Haase, 1958). Given that akathisia may still go unrecognised by psychiatrists and experienced mental health workers, it is virtually impossible that general physicians in 1955 would have correctly diagnosed the problem.

The only placebo controlled, randomised, parallel group study of reserpine in the treatment of any nervous disorder was carried out by Davies & Shepherd (1955) in people who were anxious and depressed. They demonstrated that, far from causing depression, reserpine appeared to have antidepressant properties. There is every reason to believe the findings of this study as other senior clinicians also reported that it could be useful in the treatment of subjects who were depressed (Ayd, 1958). In addition, reserpine was used in a number of centres through the 1970s and 1980s in the management of refractory depression (Price *et al*, 1987). Furthermore, Wilkins (1954), who was among those who had noted reserpine's capacity to 'depress' some individuals, also noted that "many patients become positively lyrical about their sense of well-being on the drug . . . with statements such as 'I've never felt as well', or 'I haven't felt this good for years' . . . 'Nothing bothers me any more'". This led him to state that "I have told many psychiatrists and others interested in psychotherapy that '*Rauwolfia* is good psychotherapy in pill form'".

There is another relevant dynamic. At the time, companies were able to take out process rather than compound patents. Provided one could find a different process to produce a compound, any company could produce its version of that compound, unlike today where only one company can produce fluoxetine or clozapine while these drugs are under patent. Reserpine and *Rauwolfia* were available in 26 different preparations in the late 1950s. The compound was further compromised by its molecular structure, which did not allow for ready chemical manipulations that would yield a series of patentable derivatives. Reserpine has been a compound without issue, in contrast to the almost infinitely manipulable phenothiazine nucleus. The pharmaceutical companies involved, therefore, had every incentive to let this drug go, once problems developed; nobody was going to make money in the reserpine market.

RESERPINE AND THE PATHOPHYSIOLOGY OF DEPRESSION

Considering the evidence now, it is difficult to sustain a case that reserpine causes depression. A number of implications follow. Based on the monoamine depleting effects of reserpine, there is a notion that *in some way* antidepressants act to increase amine levels. This would seem to need revision, given that, on the basis of available evidence, reserpine, which depletes monoamines, may have antidepressant properties.

More importantly, the lesson drawn from the reserpine story was that there was a monoamine lesion in depression, which antidepressants acted to correct. This is a 'magic bullet' view of antidepressant actions, which for three decades has dominated over the alternative view that actions on monoamine systems may provide therapeutic principles in the management of depressive disorders (Healy, 1997). It is now clear that actions on catecholamine and indoleamine systems may independently lead to improvements in depressive disorders and may do so by producing distinguishable behavioural changes. These aspects of antidepressant psychopharmacology have been neglected, in part owing to the apparently clear lesson that emerged from early experience with reserpine.

RESERPINE AND AKATHISIA

If we have learnt the wrong lessons from reserpine, it may nevertheless have other important lessons to teach us. The role that akathisia may play in suicides, violence and other potentially injurious behaviours has been emphasised (Van Putten, 1975). There is some evidence that akathisia/dysphoria may be more problematic in non-psychiatric populations (Healy & Farquhar, 1998), which may explain the salience of the problems produced in people with hypertension. Akathisia remains potentially the most pernicious complication of treatment with psychotropic drugs. If reserpine produced this state more than some other neuroleptics, its monoamine lowering mechanism of action may hold some clue as to the genesis of akathisia, an understanding of which might enable us reliably to produce both antipsychotics and antidepressant agents that do not produce this effect.

During the 1960s and 1970s one of the methods of selecting potential antidepressants was on the ability of candidate compounds to block the acute behavioural effects of reserpine (Costa *et al*, 1960). Rather than detect new antidepressants, this model may have resulted in a generation of compounds less likely to produce akathisia, as subsequent receptor binding and molecular biological approaches have produced agents such as fluoxetine, which are antidepressant but fail the reserpine test and produce akathisia.

RESERPINE AND RISK–BENEFIT RATIOS

The experience of clinicians who used reserpine was that in many cases of refractory schizophrenia it produced benefits comparable to those now seen with clozapine. Subsequent events have shown that agents such as clozapine, which have the potential for serious adverse effects, can be successfully deployed if those effects are understood. From this vantage point, it seems that reserpine's profile of effects could have been incorporated successfully into clinical practice, and its demise alongside the resurrection of clozapine point to a need to make careful risk–benefit assessments before drugs are removed from use. In emphasising the benefits of an agent such as reserpine, however, the risks must not be ignored. It is sometimes argued that no causal statements can be made about the role of psychotropic agents in precipitating suicides in people with schizophrenia or depression, owing to the propensity of the illnesses themselves to lead to suicide. In the case of reserpine, however, a psychotropic agent with both antipsychotic and antidepressant credentials did lead to suicide in

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a number of subjects and the drug can be implicated causally in that these were people with hypertension not suffering from a psychiatric illness. It is a truism that the more risks an agent poses, the greater the caution needed in extending its use beyond those who clearly benefit; the case of reserpine suggests that where the potential for benefits falls, risks may even escalate.

DAVID HEALY, FRCPsych, MARIE SAVAGE, MBBS, North Wales Department of Psychological Medicine, Hergest Unit, Bangor

Correspondence: D. Healy, North Wales Department of Psychological Medicine, Hergest Unit, Bangor, LL57 2PW

(First received 4 September 1997, final revision 16 December 1997, accepted 16 December 1997)

REFERENCES

Achor, R. W. R., Hanson, N. O. & Gifford, R. W. (1955) Hypertension treated with rauwolfia serpentina (whole root) and with reserpine. Controlled study disclosing occasional severe depression. *Journal of the American Medical Association*, **159**, 841–845.

Ayd, F. J. (1958) Drug induced depression – fact or fallacy. *New York State Journal of Medicine*, **58**, 354–356.

Bernstein, S. & Kaufman, M. R. (1960) A psychological analysis of apparent depression following rauwolfia therapy. *Journal of Mount Sinai Hospital*, **27**, 525–530.

Costa, E., Garrattini, S. & Valzelli, L. (1960) Interactions between reserpine, chlorpromazine and imipramine. *Experientia*, **15**, 461–463.

Davies, D. L. & Shepherd, M. (1955) Reserpine in the treatment of anxious and depressed patients. *Lancet*, *ii*, 117–121.

Deniker, P. (1983) Discovery of the clinical use of neuroleptics. In *Discoveries in Pharmacology* (eds M. J. Parnham & J. Bruinvels), pp. 163–180. Amsterdam: Elsevier.

Faucett, R. L., Litin, E. M. & Achor, R. W. P. (1957) Neuropharmacologic action of rauwolfia compounds and its psychodynamic implications. *American Medical Association Archives of Neurology and Psychiatry*, **77**, 513–518.

Ferguson, J. T. (1955) Treatment of reserpine-induced depression with a new analeptic: phenidylate. *Annals of the New York Academy of Sciences*, **61**, 101–107.

Freis, E. D. (1954) Mental depression in hypertensive patients treated for long periods with large doses of reserpine. *New England Journal of Medicine*, **251**, 1006–1008.

Genest, J., Adamkiewicz, L., Robillard, R., *et al* (1955) Clinical use of reserpine. *Canadian Medical Association Journal*, **72**, 483–489.

Hasse, H.-J. (1958) The role of drug-induced extrapyramidal syndromes. In *Psychopharmacology Frontiers* (ed. N. S. Kline), pp. 197–208. Boston, MA: Little Brown.

Harris, T. H. (1957) Depression induced by Rauwolfia compounds. *American Journal of Psychiatry*, **113**, 950.

Healy, D. (1997) *The Antidepressant Era*. Cambridge, MA: Harvard University Press.

—— & Farquhar, G. M. (1998) Immediate effects of droperidol. *Human Psychopharmacology*, **13**, in press.

Jensen, K. (1959) Depressions in patients treated with reserpine for arterial hypertension. *Acta Psychiatrica Scandinavica*, **34**, 195–204.

Kass, I. & Brown, E. B. (1955) Treatment of hypertensive patients with rauwolfia compounds and reserpine: depressive and psychotic changes. *Journal of the American Medical Association*, **159**, 1513–1516.

Lemieux, G., Davignon, A. & Genest, J. (1956) Depressive states during rauwolfia therapy for arterial hypertension. A report of 30 cases. *Canadian Medical Association Journal*, **74**, 522–526.

Muller, J. C., Pryor, W. W., Gibbons, J. E., *et al* (1955) Depression and anxiety occurring during rauwolfia therapy. *Journal of the American Medical Association*, **159**, 836–839.

Price, L. H., Charney, D. S. & Heninger, G. R. (1987) Reserpine augmentation of desipramine in refractory depression: clinical and neurobiological effects. *Psychopharmacology*, **92**, 431–437.

Sarwar-Foner, G. J. & Ogle, W. (1955) Psychosis and enhanced anxiety produced by reserpine and chlorpromazine. *Canadian Medical Association Journal*, **74**, 526–532.

Schroeder, H. A. & Mitchell-Perry, H. (1955) Psychosis apparently produced by reserpine. *Journal of the American Medical Association*, **59**, 839–840.

Smirk, F. H. & McQueen, E. G. (1955) Comparison of rescinamine and reserpine as hypotensive agents. *Lancet*, *2*, 115–116.

Vakil, R. J. (1949) Clinical trial of Rauwolfia serpentina in essential hypertension. *British Heart Journal*, **2**, 350–355.

Van Putten, T. (1975) The many faces of akathisia. *Comprehensive Psychiatry*, **16**, 43–47.

Wallace, D. C. (1955) Treatment of hypertension. Hypotensive drugs and mental changes. *Lancet*, *2*, 116–117.

Wilkins, R. W. (1954) Clinical usage of rauwolfia alkaloids, including reserpine. *Annals of the New York Academy of Sciences*, **59**, 36–44.

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