

MENTAL DEPRESSION IN HYPERTENSIVE PATIENTS TREATED FOR LONG PERIODS WITH LARGE DOSES OF RESERPINE*

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THE introduction of *Rauwolfia serpentina* into this country by Wilkins and Judson¹ and the purification of an active alkaloid, reserpine (Serpasil), has led to the widespread clinical use of the latter drug not only in hypertension^{2,3} but also in neuropsychiatric conditions.⁴ The purpose of this report is to describe the development of psychiatric complications in hypertensive patients treated with large doses of reserpine for long periods.

CASE REPORTS

CASE 1. Mrs. I.K., a 54-year-old widow, had mild hypertension for 1 year associated with headache and substernal pain. Since the death of her husband 2 years previously she had been more emotional and easily upset than formerly. The blood pressure was 190/105. The fundi showed Grade 1 changes; the heart was normal in size, and examination of the urine was negative.

The patient was treated with reserpine, 0.5 mg. twice daily, and alkavervir (Veriloid), 4 mg. 3 times daily, the average blood pressure falling to 165/100. There was no change in symptomatology until 4 months after treatment was instituted, when, after a vacation trip to visit her mother, she began to feel extremely depressed. She was conscious of "everything in her body" and was worried about her blood pressure. She did not believe that life was worth living. She wanted to remain at home and was incapable of enjoying any of the pursuits that had formerly given her pleasure.

Reserpine and alkavervir were withdrawn, and phenobarbital, 60 mg. 4 times daily, was substituted. She improved slowly for the succeeding 2 months and had remained free of depression when last seen six months later.

CASE 2. Severe hypertension developed in W.H., a 44-year-old college professor, over a period of 3 years. When he was first seen in 1950 the blood pressure was 240/140, the fundi showed Grade 3 changes, with hemorrhages and exudates, and the heart was greatly enlarged; the urine gave a ++ test for albumin.

He was treated with alkavervir for 6 months, and then parenteral administration of hexamethonium was substituted. There was remarkable improvement, with reduction of average blood pressure to 160/100, regression of changes in the optic fundi to Grade 1, decrease in the heart size and clearing of the albuminuria. He returned to a full-time schedule of teaching, feeling better than at any time in the past 5 years.

In September, 1953, the treatment was changed to pentolinium tartrate (pentapyrrolidinium, or M&B 2050), 100 mg. orally 3 times daily, and reserpine, 0.5 mg. 3 times daily. Sleepiness and lethargy developed so that after 2 weeks the dosage was reduced to 0.5 mg. twice daily.

The patient continued to feel extremely well until Jan-

uary, 1954, when he became severely depressed. He lost all self-confidence and became fearful of meeting people socially, including his close friends, and excessively introspective and lost all enthusiasm for his work. He debated whether to escape into alcoholism but did not do so. He did not want to leave his room or to meet anyone. He wished for death but did not contemplate suicide.

He did not manifest anxiety so much as inertia of intellect and loss of capacity to enjoy life. His appetite remained good during this period, and he gained weight despite his depressed outlook. His ability to concentrate was markedly retarded in that he fumbled for words during lectures and was unable to digest the current literature in his field.

He lived in another city and did not communicate his intellectual and emotional change to this clinic. Nevertheless, there was a slight improvement in the spring of 1954 despite the fact that he continued to take reserpine. In June, when he was readmitted to the hospital for a checkup, reserpine was withdrawn, but pentolinium tartrate was continued. He began to improve dramatically after 48 hours and within a week was restored to his usual mental and emotional vigor.

CASE 3. Mrs. R.K., a 41-year-old housewife, had hypertension of 5 years' duration. The blood pressure was 220/135, and the fundi showed Grade 3 changes, with hemorrhages but no exudates. Cardiac and renal findings were not significantly abnormal. She was hospitalized and treated with alkavervir, 4 mg. 3 times daily, and reserpine, 0.5 mg. twice daily. After 1 week the dosage of reserpine was reduced to 0.25 mg. once daily.

After discharge from the hospital the home recordings of blood pressure averaged 150/100. The patient felt well until 4 months after treatment was instituted, when she became "chronically unhappy" and "nothing pleased her" and yet she could find no external reason for her dissatisfaction. Whereas previously she had always been extremely active and enjoyed shopping tours and club visits with her friends, she did not want to leave the house and did not enjoy her friends. Ordinary household duties were accomplished with great effort. There was no loss of appetite and little anxiety associated with this depression. The dosage of reserpine was reduced to 0.1 mg. a day for 2 weeks, but the symptoms persisted. Reserpine, but not alkavervir, was then discontinued, and within 1 week she returned to her previously happy emotional and vigorous physical state.

CASE 4.* J.J., a 60-year-old executive, had had hypertension for 10 years. In the past year the blood pressure had been about 200/120, but he had no hypertensive symptoms. He always had been rather tense and anxious and suffered from a moderate degree of claustrophobia. The fundi showed Grade 1 changes; the heart was not enlarged, and urinalysis was negative. The office recording of blood pressure was 210/115, but several recordings at home averaged 180/105.

He was treated with an extract of *Rauwolfia* (Rauwiloid), 4 mg. twice daily for 1 month, and since there was no change in blood pressure alkavervir, 5 mg. twice daily, and reserpine, 0.5 mg. twice daily, were substituted. On this regimen the blood pressure at home varied between 140/90 and 180/100. Because of continued feeling of emotional tension the dosage of reserpine was increased to 1.0 mg. twice daily after 1 month. The patient felt calmer and was quite well for the ensuing 2 months, when, immediately after his daughter's marriage, an acute depression with agitation developed. He was afraid to leave the house without his wife. His claustrophobia became so severe that he would not step into an elevator. He thought that he had become a burden to everyone and lay awake at night contemplating suicide.

Reserpine, but not alkavervir, was discontinued, but because of the severity of the symptoms the consulting psy-

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chiatrist decided to give him electroshock therapy without delay. After a short course of treatment the patient began to improve slowly and was soon back at work.

CASE 5. H.B., a 52-year-old retired policeman, first had malignant hypertension in 1950. When he was seen in the hospital in 1950 the blood pressure was 230/140, the fundi showed Grade 4 changes, and the heart was enlarged, with pulmonary congestion; there was impairment of renal function without nitrogen retention.

He responded well to treatment with hexamethonium subcutaneously and 1-hydrazinophthalazine (Apresoline) orally and remained on that regimen until May, 1953, when pentolinium tartrate by mouth was substituted for the subcutaneous administration of hexamethonium. At this time reserpine, 0.25 mg. 3 times daily, was also given, this regimen being continued for approximately 1 year, during which the average blood pressure was 165/95. He felt quite well.

On April 4, 1954, because of the development of easy fatigability and lassitude, the dosage of reserpine was reduced to 0.25 mg. once daily. Nevertheless, he continued to feel tired and also became depressed. He did not wish to leave the house, but at home he did not enjoy television, working in the garden or any of the other pursuits in which he had formerly taken pleasure. He woke up in the early hours of the morning and during this time considered various methods of committing suicide. Whereas he had previously been affably aggressive and talkative he now appeared quiet, uncertain and depressed. Reserpine was discontinued, and he was followed by a psychiatrist. He improved slowly for several weeks but, when last seen, had still not returned completely to his previous personality state.

DISCUSSION

Although several drugs were used in these cases the evidence as a whole strongly suggests that the emotional disorders reported were brought on by reserpine. Reserpine was the only agent used in all the patients, some receiving veratrum alkaloids and others

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pentolinium bitartrate with or without 1-hydrazinophthalazine. Furthermore, no psychiatric complications of the kind described in these case reports were observed in patients taking any of the other antihypertensive agents without reserpine. Finally, in 4 cases the depression cleared after reserpine had been discontinued. Thus, it appears that reserpine rather than any of the other drugs was the most important contributing factor in the development of the depressed state.

The emotional reaction of several patients did not appear to be that of a true anxiety depression. They manifested withdrawal from the environment, lethargy and unhappiness but not anxiety. In addition, anorexia and weight loss did not occur. Nevertheless, all considered life not worth living, and 2 of them contemplated suicide.

Lesser degrees of depression have frequently been encountered in other patients in this clinic. Common symptoms, often so mild as to pass without comment unless specifically asked for, were lack of ambition, crying spells, introspection and lethargy.

It is worthy of note that the dosage of reserpine in all cases except 1 was maintained at a higher level

than that advised customarily, being 1.0 mg. a day in 2 and 1.5 and 2.0 mg. a day, respectively, in 2, only 1 of the patients being maintained on a dose of 0.25 mg. a day. It is also noteworthy that in every case the drug had been administered continuously for two months or longer before the symptoms of mental depression appeared. In 1 case the appearance of the syndrome was delayed for approximately a year after the institution of treatment. Once depression developed, however, reduction of the daily dosage from 0.25 to 0.1 mg. (Case 3) and from 1.0 mg. to 0.25 (Case 5) failed to relieve the symptoms, and complete withdrawal of the drug was necessary.

It is also apparent that disturbing environmental factors may have played a part in the development of the syndrome. In Case 1 depression developed after the patient visited her mother, and in Case 4 it followed the marriage of the patient's daughter. In the remaining cases, however, no obvious precipitating factors were evident.

Since reserpine is being used widely at present for the treatment of mental illness, as well as hypertension, it seems appropriate to call these cases to the attention of the medical profession, so that accumulated experience can confirm or reject the implication of this report that reserpine caused the psychiatric condition described. Although similar psychiatric complications were not observed in patients treated with other *Rauwolfia* preparations it must be emphasized that the great majority of the patients in this clinic were treated with reserpine rather than with other extracts. Therefore, the experience with other drugs containing *Rauwolfia* is too limited for one to pass judgment on whether they are also apt to produce this syndrome.

SUMMARY AND CONCLUSIONS

Five cases of mental depression are described. These developed in hypertensive patients after several months of continued treatment with reserpine in dosage varying from 1.0 to 2.0 mg. a day in 4 and 0.25 mg. a day in 1 of the cases. Maintenance doses of this agent should be kept as low as possible, preferably below 0.25 mg. a day, to minimize the development of this syndrome.

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