2. To co-operate in answering a simple questionnaire designed to furnish information on the influence of various factors on the results of the hæmoglobin determinations which will assist the panel in its long-range plans for making this standard available on a national scale.
3. To co-operate in the analysis and reporting of (a) an unknown solution of cyanmethæmoglobin, and (b) an unknown sample of blood.

The Standard for Distribution, consisting of the three solutions described above, will be packaged as a single unit. Details of the procedure for the determination of hæmoglobin as cyanmethæmoglobin, as well as details of the procedure for calibrating another method in terms of the cyanmethæmoglobin standard, will be furnished with the standard.

Distribution will be made to civilian laboratories by the College of American Pathologists, 203 North Wabash Avenue, Chicago, Illinois; to military and government laboratories by the Army Medical Service Graduate School, the Navy Bureau of Medicine and Surgery, the Air Force Surgeon General's Office, and the Veterans' Administration; and *to laboratories in Canada through the Division on Medical Research, National Research Council, Ottawa, Ontario.* Cooperating laboratories are requested to apply to the distributing agency with which they are most closely associated. Because of limitation in the number of sets of the standard available, distribution will be determined by priority of application and willingness to comply with the conditions listed above. Application for standards will assume acceptance of these conditions.

It is estimated that the Standard will be ready for distribution by April 15, 1955.

This plan has been drafted by the *ad hoc* panel on the establishment of a hæmoglobin standard of the Division of Medical Sciences, National Academy of Sciences—National Research Council.

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AN EXTRAPYRAMIDAL SYNDROME WITH RESERPINE*

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THIS PAPER REPORTS the appearance of extrapyramidal signs and symptoms, ranging in severity from cogwheel rigidity in the upper limbs to a state resembling a complete Parkinson syndrome, in 12 of 19 patients receiving the rauwolfia alkaloid reserpine. The patients receiving the drug consisted of 11 women and eight men. Of those developing the extrapyramidal symptoms, nine were women and three were men. The patients ranged in age from 19 to 61.

No other medication or physical treatment was given with reserpine or at the time these symptoms developed. None of the patients showed any initial liver malfunction as measured by the blood alkaline phosphatase level. Of those developing extrapyramidal symptoms, seven had received no other medication before, one had had chlorpromazine four months previously, and four had had electro-convulsive therapy before receiving reserpine. Examination of all patients at the start of reserpine treatment gave no evidence of neurological impairment.

With regard to *dosage*, the amounts of reserpine administered before the appearance of the extrapyramidal symptoms varied considerably from one patient to another. All patients were started routinely on an initial daily dose of 5 mgm. intramuscularly and 3 mgm. orally. This dosage was subsequently adjusted upwards or downwards, depending upon the clinical status of the patient. The amounts of reserpine given thus ranged from 3 to 13 mgm. intramuscularly and from 0.5 mgm. to 5 mgm. orally, daily over the period of treatment. The total amount of reserpine administered intramuscularly and orally before the appearance of cogwheel rigidity was between 21.5 and 193.0 mgm. The total amount administered before the appearance of the Parkinson syndrome was between 54.0 mgm. and 339.5 mgm. All but one patient were on combined intramuscular and oral administration. In this one instance the extrapyramidal signs and Parkinson picture appeared while the patient was on oral administration, receiving 5 mgm. daily for 11 days.

The *duration of treatment* before the appearance of cogwheel rigidity was between three and 19 days, and, before the more complete extrapyramidal syndrome, between 10 and 23 days. There is thus a very wide range of individual

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difference in the relationship between the appearance of signs and the dosage and duration of treatment.

The first symptom to appear is cogwheel rigidity in the upper limbs, followed by loss of facial mobility and expression and appearance of the typical mask-like facies. These signs are then followed by tremor and rigidity in the upper and lower limbs, loss of associated movements on walking, shuffling gait and monotonous voice. Cogwheel rigidity appeared in 12 of the patients, and the Parkinson syndrome in eight of the 12.

These signs are usually accompanied by marked salivation and drooling, by gain of weight and by complaints of increased frequency of urination. It was also noted in all patients developing this Parkinson syndrome that, regardless of the severity of the overt symptoms and despite the appearance of apathy with mask-like facies, they remained in excellent contact, alert and with no gross impairment of intellectual function. By the time the extrapyramidal symptoms had appeared, the characteristic initial period of somnolence had passed off, and in fact the patients tended quite frequently to complain of feeling restless. Though usually definitely less reactive and more "tranquil," they showed none of the mental apathy or lethargy suggested at first sight by the mask-like facies and shuffling gait. Overt alteration of mood tended to be in the direction of mild euphoria with easy smiling and laughing, even with extrapyramidal symptoms. This was frequently associated, however, in quite anomalous fashion, with subjective reports of depression or of "feeling terrible."

The syndrome showed no sign of remission with continued treatment. Instead, it was slowly progressive and increasingly severe, leading to a picture of almost board-like generalized muscular rigidity. It was necessary to alter administration of the drug because of the extrapyramidal signs, which would gradually diminish or disappear. In some cases, it has been possible to reduce the severity of the extrapyramidal signs and to halt their progression by reduction in dosage. Thus, despite those individual differences already noted, there appeared to be a rough but direct relationship between the level of total daily dosage and the appearance and severity of the various signs.

Finally, it should be pointed out that these signs occurred with much larger doses of reserpine than are ordinarily given for other purposes, such as the medical treatment of hypertension. Papers reporting the use of the drug in such cases either do not mention such signs as those described here, or state specifically that the drug is "remarkably well tolerated over prolonged periods of time, and free from toxic or even very serious side-effects."[1] All the cases treated in this series have been acutely disturbed and agitated and presented problems in ward management. The doses used were those required to reduce this overactivity and were up to ten times as large as those used in the treatment of hypertension.[2, 3]

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CLINICAL EXPERIENCE WITH PSYCHIATRIC PATIENTS ON RESERPINE – PRELIMINARY IMPRESSIONS*

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SO FAR, 19 psychiatric patients have been treated with the rauwolfia alkaloid reserpine, and the study is continuing. These patients, all severely disturbed and selected because they presented problems in ward management, were characterized by over-activity, agitation, and anxiety, frequently accompanied by delusions, hallucinations, or severe dissociation. Diagnoses include eight cases of paranoid states, two of undifferentiated schizophrenic reactions, three of dissociated states with hallucinations or delusions, two of severe anxiety reactions, and one case each of hysteria, barbiturate addiction, depression and psychopathy. There were 11 women and eight men, ranging in age from 19 to 61.

Dosage.—The initial routine dosage is 5 mgm. intramuscularly and 3 mgm. orally, daily, in divided doses of 2.5 mgm. intramuscularly and 1 mgm. orally. This dosage was subsequently adjusted according to the clinical state of the patient, the daily dosage varying over the total period of treatment for all patients between three and 13 mgm. intramuscularly and between 0.5 and 5 mgm. by mouth, giving an average daily maintenance dose of 7 mgm. intramuscularly and 3 mgm. orally.

Duration of treatment.—The duration of treatment ranged from six to 35 days. This has not depended solely on symptomatic improvement but also upon other factors, such as the appearance of side-effects or toxicity, or upon the failure of the patient to show some reduction in activity.

*From the Allan Memorial Institute, Royal Victoria Hospital and McGill University, Montreal, P.Q. The material used was in the form of Serpasil-Ciba, provided through the courtesy of Dr. C. Walter Murphy of Ciba Company Ltd., Montreal.

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