The Aminochromes and Schizophrenia

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Introduction

The adrenochrome hypothesis of the etiology of schizophrenia was introduced almost two decades ago. It aroused considerable interest and, because of the controversial field into which it was introduced, widespread adverse criticism. Today it is still neither proved nor disproved. However the studies of the last five years have clarified a few points.

Our studies were designed to define the metabolic changes of catecholamines in human blood and the effects of the changed chemicals on the blood. Accordingly, a method was developed which involves the synthesis of the expected metabolites, the incubation of the chemicals with blood or with plasma and the study of the changed chemicals after incubation in the plasma by means of differential ultraviolet and visible spectroscopy. This method hereafter will be referred to as the Hegedus method.

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Indole Derivatives

First the indole derivatives obtained from epinephrine were studied, since previous workers had shown that the enzymes of the VMA pathway of epinephrine degradation are not active in blood (Tryding et al., 1969). The indole derivatives of epinephrine, adrenochrome and adrenolu-tin-monohydrate were synthesized in our laboratory. Studies on adrenolutin had been retarded for years by the widespread impression that stable adrenolutin-mono-hydrate could not be made. This is no longer true; work done in Heacock's and our laboratories established a method by which adrenolutin-monohydrate can be made in a stable form (Heacock and Mahon, 1958; Hegedus and Altschule, 1967b).

Blood Aminochromes

Our studies suggest that aminochromes and their derivatives, plasma-soluble mela-nins or rheomelanins, are present in the human blood (Hegedus and Altschule, 1970a and 1970c), however, they have not yet been isolated and identified. Consequently there is no method of measuring blood aminochromes unless the recently proposed method of Professor **R.** T. Houlihan

proves itself. Hence no statement can be made as regards quantities in different subjects. Future work will perhaps eliminate these uncertainties.

Adrenochrome

The transformation of epinephrine to adrenochrome added to human plasma or serum is well documented (Hegedus and Altschule, 1968; Altschule and Nayak, 1970) (See Fig. 1). The subsequent fate of adrenochrome in human plasma was not worked out until recently (Hegedus and Altschule, 1967a, 1968). We showed that adrenochrome added to normal human heparinated or oxalated plasma changed to a substance even in the frozen state with ultraviolet and visible spectra and with fluorescence of adrenolutin that has been dissolved in the same plasma. Thus in Figure 2, Curve A shows the ultraviolet and visible spectra of authentic adrenochrome that had been dissolved in plasma immediately before the spectra were made. Curve B shows the spectra obtained when adrenochrome was dissolved in plasma, kept frozen until the color changed to yellow-brown and then thawed for study. Curve D shows the spectrum of authentic adrenolutin made immediately after it had been dissolved in plasma. Curves B and D are almost identical. Curve C was obtained after adrenochrome had been incubated in the same plasma at 37° for 30 minutes (Hegedus and Altschule, 1967a). The main adrenolutin peak at circa 320 mu was decreasing and a new maximum at circa 280 mu was developing. This circa 280 mu shoulder obtained by differential spectroscopy in the experiments is significant in that it indicates the beginning of the change of adrenolutin to rheomelanin.

As Figure 3 shows, the incubation of epinephrine, adrenochrome and adrenolutin separately in aliquots of the same plasma for 24 hours gives rise to virtually the same spectral curves. The excitation maxima of all three rheomelanins are around 340 and 404 mu, the fluorescence maxima are around 482 mu.

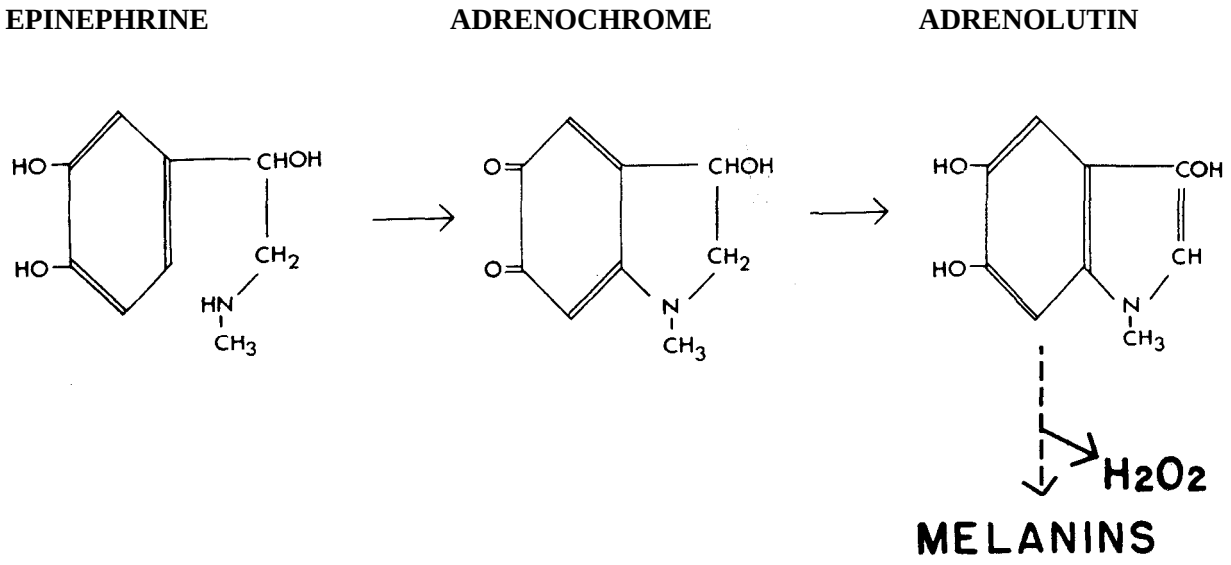

Figure 1. The indole pathway of catecholamine metabolism.

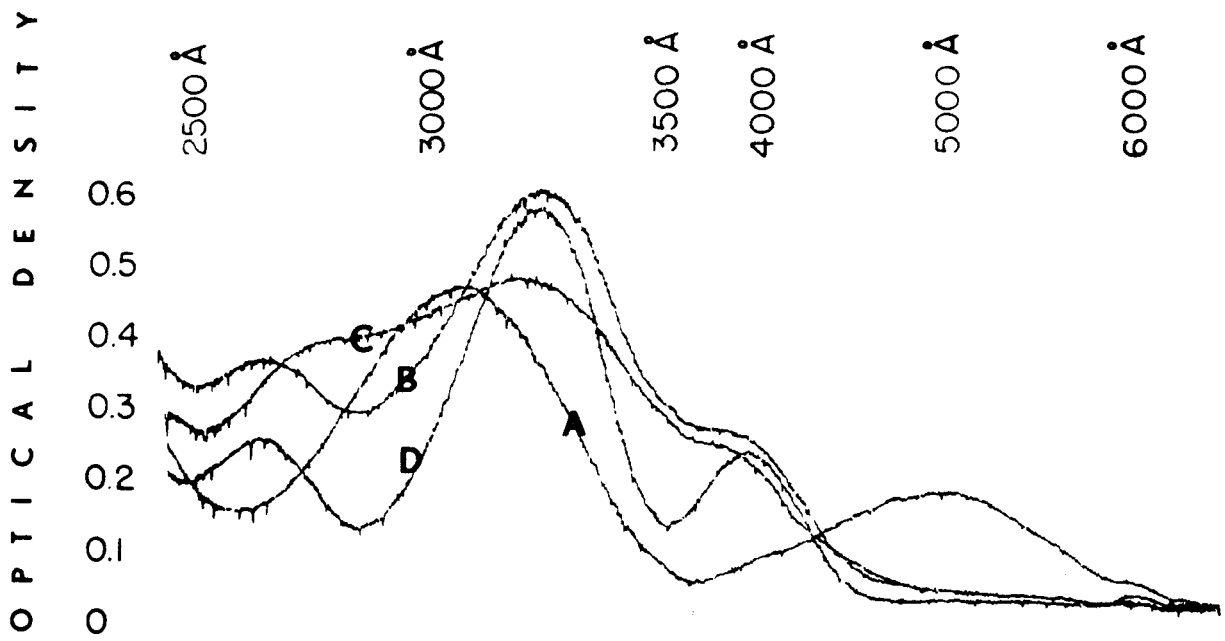

Figure 2. Transformation of adrenochrome to adrenolutin in human plasma.

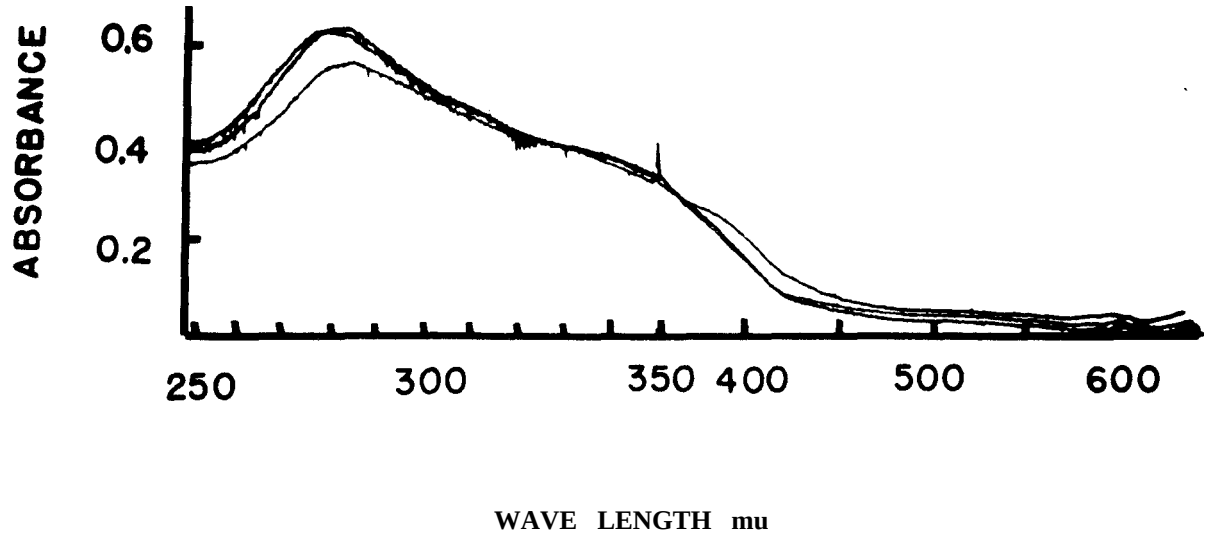

Figure 3. Formation of identical rheomelanins from epinephrine, adrenochrome and adrenolutin in human plasma.

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The possibility that adrenochrome can exist in blood plasma except for a short time is remote. Its period of existence is short and the compound is soon isomerized to adrenolutin. This in turn is rapidly polymerized to rheomelanin, a substance with strong free-radicle activity; hydrogen peroxide might be liberated during the polymerization and this would likewise be toxic, at least to some tissues, e.g. brain, which unlike the blood lacks enzymes for inactivating it.

Except for small effects on dopamine, blood shows no ability to degrade catecholamines by the monoamine oxidase mechanism (Tryding et al., 1969); epinephrine and norepinephrine if degraded in the blood stream probably follow the indole pathway. In addition, the catecholamine and dopa cyclization that may occur in the solid tissues may be a potential source of aminochromes that might be delivered to the circulating blood. The cyclization of catecholamines in solid tissues, including the brain, has obvious implications as regards tissue melanin formation.

Rheomelanins

The formation of rheomelanin deserves some comment. In the studies made here only the catecholamines, dopa and a few of their derivatives polymerized to form rheomelanins. It appears that the two free 3, 4 hydroxyl groups on the benzene ring are necessary for the formation of rheomelanins. Although melanins may form slowly from 5, 6 dihydroxyindole after 0-methylation at carbon 6 (Axelrod and Ler-ner, 1963), there is no indication that metanephrine or normetanephrine produce rheomelanins (Hegedus and Altschule, 1970c); this seems to be owing to then-inability to form indole derivatives.

Incubation of normal blood with catecholamines, aminochromes, or dopa causes the appearance in plasma of a spectral peak at circa 400 mu indicative of hemolysis (See Fig. 4). This peak designates hemoglobins and porphyrins. The mechanism of the hemolysis is not established. All the rheomelanins prepared by us have free radical activity (Polis, 1969) in common with other melanins (Mason et al., 1960; Van Woert et al., 1967). Free radicals not only hemolyze red blood cells but can change the hemoglobin to other hemes and to porphyrins (Rowland et al., 1968). Adrenolutin has actually been shown to change hemoglobin to porphyrin (Veech, 1968). Aside from these facts little is known about the hemolysis that accompanies rheomelanin formation.

Excessive Hemolysis

When heparinated or oxalated chronic schizophrenic blood is incubated with catecholamines, aminochromes, or dopa excessive hemolysis develops in many cases (Hegedus and Altschule, 1970b; Hegedus and Altschule, 1970e). (See Fig. 5, 6, 7)The excessive hemolysis noted with these chemicals was not affected when patients took placebos. It did however disappear when both of two patients so studied improved. The excessive hemolysis is evidently a reflection of a relative lack of some protective substance in schizophrenic blood because the differences between normal and schizophrenic bloods are not evident when smaller amounts of the aminochromes tested are used. When oxalated or heparinated normal and chronic schizophrenic bloods were incubated without the chemicals no significant differences were evident. These observations on excessive hemolysis provided the bases of a recently developed method for the routine study of psychotic patients (Hegedus et al., 1970). The rheo-melanins or their precursors, from adrenochrome, from adrenolutin and from dopamine were found to cause the greatest differences in hemolysis between normal and chronic schizophrenic blood, therefore these chemicals were chosen for this test.

The Aminochrome-rheomelanin Hypothesis

At present no conclusion can be reached concerning the possibility that schizophrenic patients make more aminochromes than do normal persons. What can be stated, however, is that one tissue, i.e., the blood of most schizophrenic patients is unusually susceptible to the toxic actions associated with rheomelanin formation from catecholamines, from their indole derivatives and from dopa. Since the blood is perhaps the least susceptible of the tissues, the possibility that brain tissue is even more susceptible is a strong one. Instead of using the term *adrenochrome hypothesis* it would be more appropriate to call it the *aminochrome-rheomelanin hypothesis.*

Studies are now under way to quantitate the observed abnormality.

Figures 5, 6 and 7 follow

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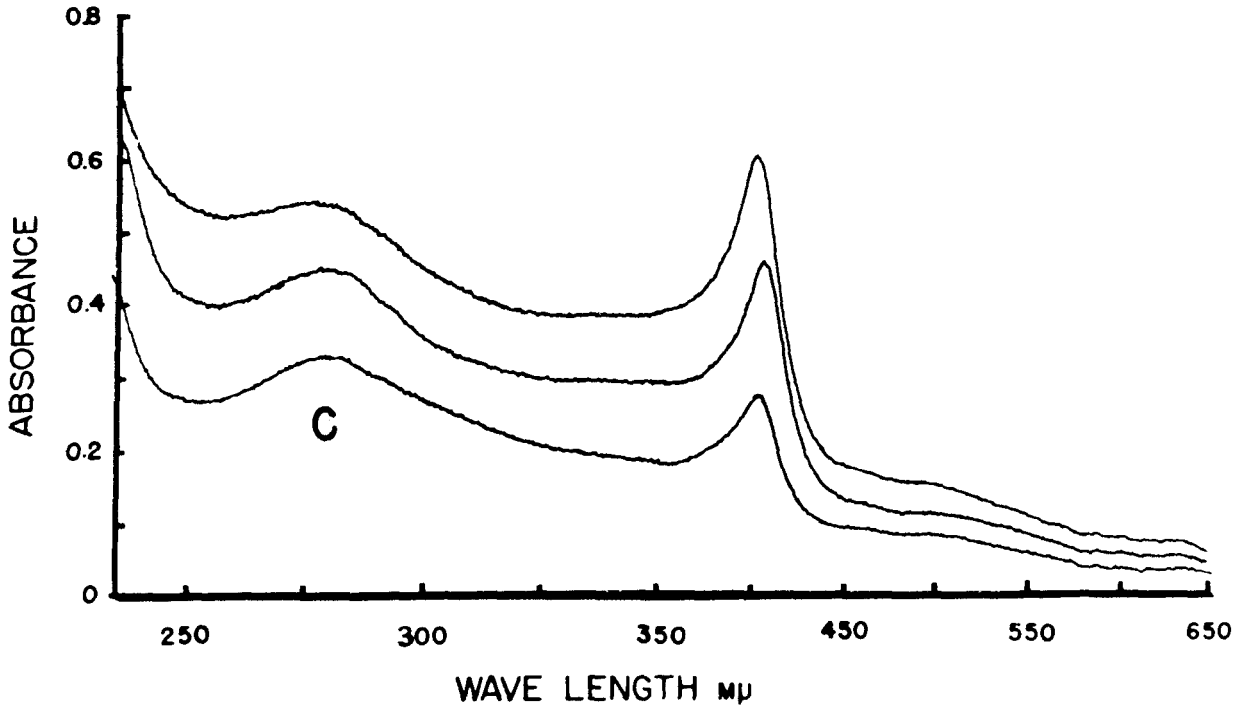

Figure 4. Hemolysis during incubation of human blood with epinephrine, adrenochrome and adrenolutin. Slightly different concentrations of the three chemicals were used. The peak at circa 400 mu indicates hemolysis.

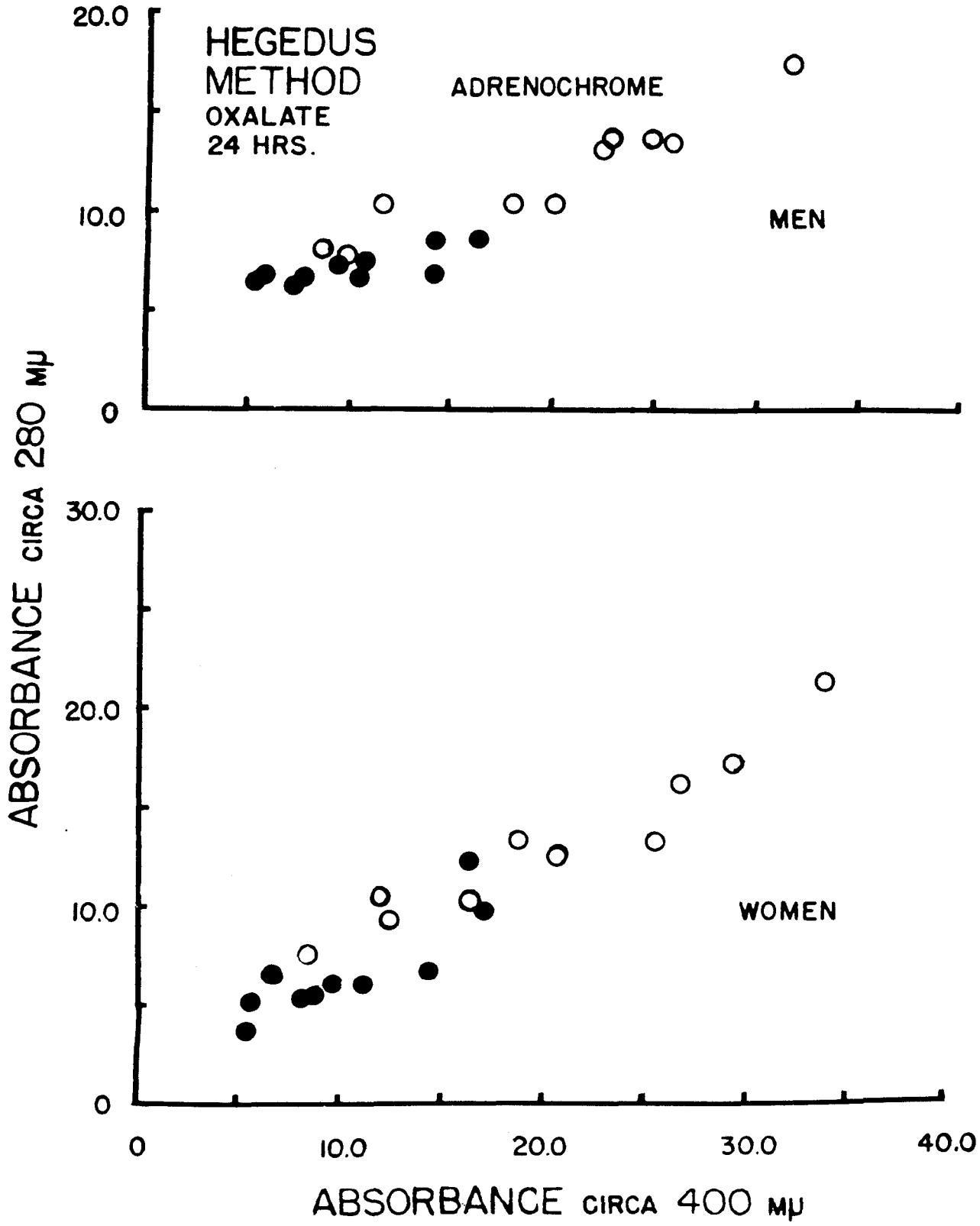

Figure 5. Hemolysis (absorbance circa 400 mu) and rheomelanin formation (absorbance circa 280 mu) during incubation of blood with adrenochrome. Solid dots indicate normal subjects; open circles indicate patients.

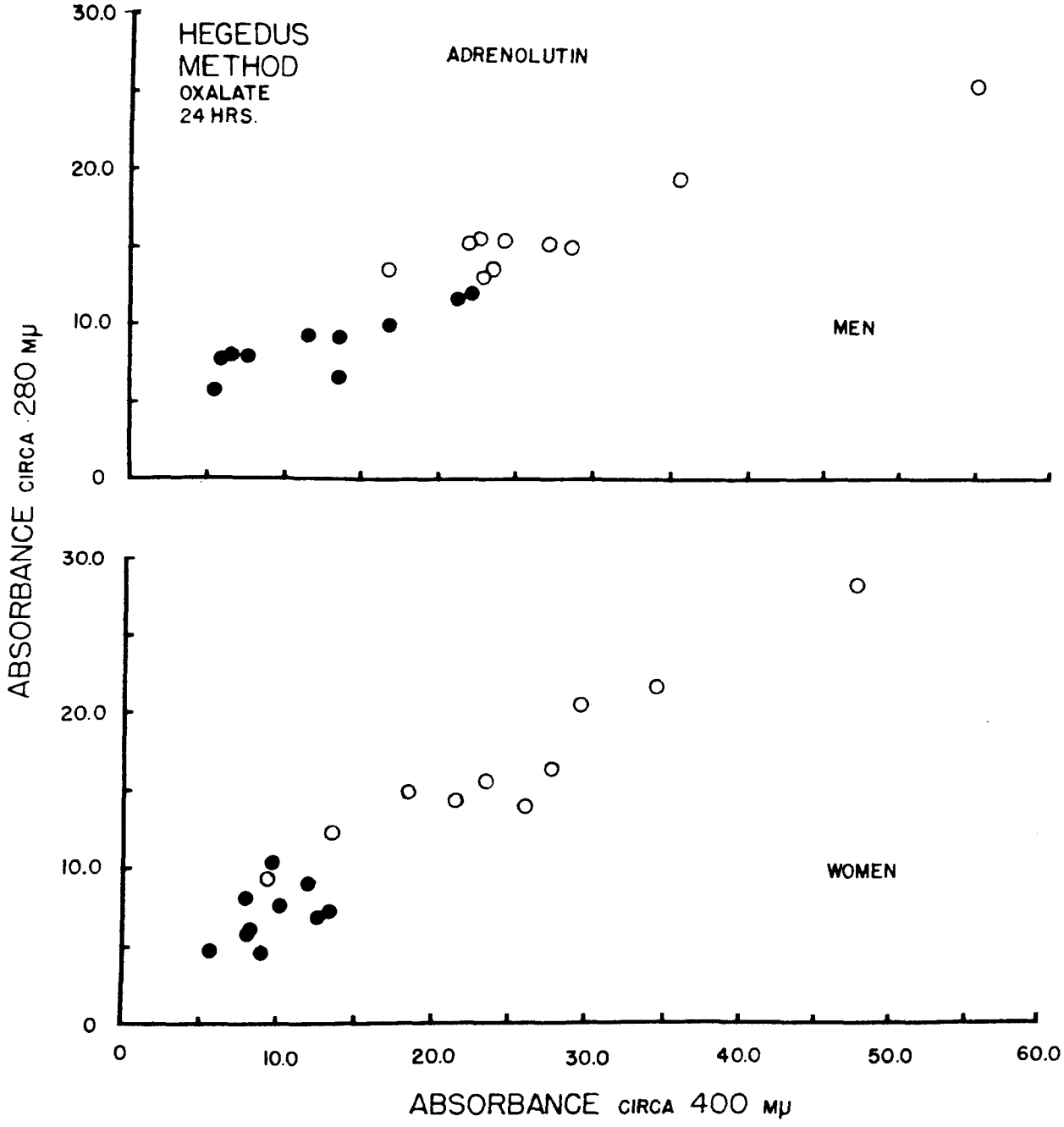

Figure 6. The same after incubation with adrenolutin.

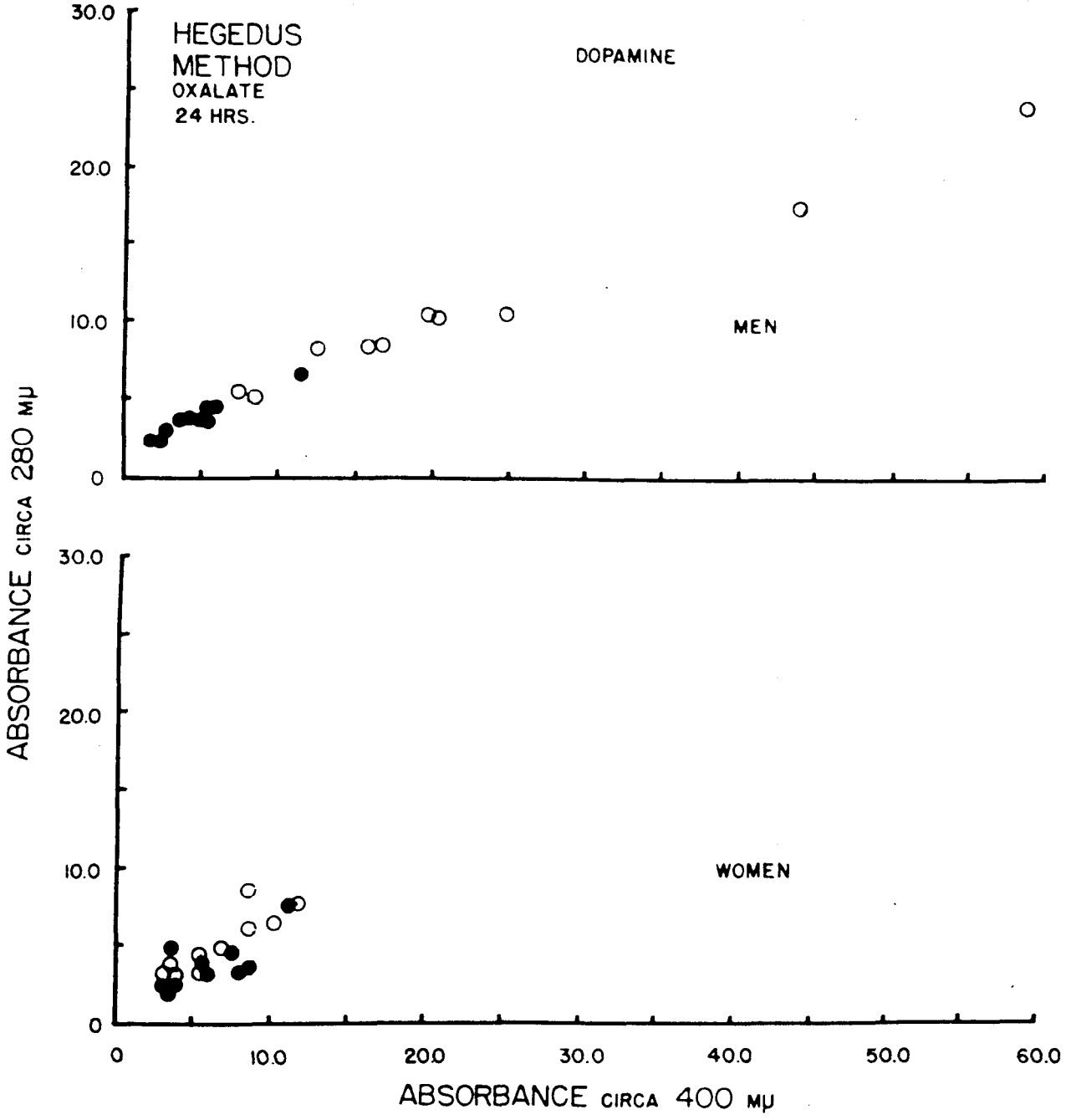

Figure 7. The same after incubation with dopamine.