As has been emphasized by Haines (1950), all the methods of treatment at present available for hyperthyroidism are far from ideal and further investigations on methods of controlling Graves' disease are still necessary. Therefore great interest has been aroused by the studies of Perrault et al. (1949), who originally observed an amelioration in the crisis and recent exophthalmos of Graves' disease following the administration of p-hydroxypropiophenone (PHP). Based on the assumption of a causal role of the pituitary thyrotrophic hormone (TSH) in the pathogenesis of these symptoms, they postulated that PHP inhibits the production of TSH. Subsequently Perrault (1950) used PHP in the treatment of many cases of Graves' disease and claimed rapid and dramatic improvement.

Perrault's statements have received some experimental support. Loeper et al. (1951) and Lacassagne et al. (1951) found that PHP given to rats was able to prevent the development of goiter as a result of propylthiouracil administration, which has been shown to augment the production of TSH. Lacassagne et al. (1951) also reported a decrease in the height of the cells of the thyroid follicular epithelium, with enlargement of the
follicular lumen and accumulation of colloid stores, after treatment of mice with PHP. Using the Warburg respirometer as a means of following quantitatively the oxygen absorption during the oxidation of tyrosine, Ghiretti & Boeri (1951) demonstrated that PHP inhibits the oxidation of tyrosine by tyrosinase in vitro when present in appropriate concentration; and since PHP and tyrosine have a similar structure, the suggestion was made that PHP may be a competitive antagonist of tyrosine.

Observations in animals by other groups of investigators, however, failed to substantiate that PHP produces a depressor action on the pituitary secretion of TSH. Guillemin (1951), Money et al. (1951), Schaffenburg et al. (1951) noted that PHP given to rats did not produce any significant difference in thyroid weight or macroscopic and histological features. Di Ferrante & Zilli (1951), Money et al. (1951), Schaffenburg et al. (1951) were unable to confirm that the development of goiter in animals receiving thiouracil or propylthiouracil is prevented by PHP. Lederer (1951) found that PHP did not lower the production of TSH by the hypophysis of thyroidectomized rats. Studies by Money et al. (1951) also indicated that the administration of PHP to rats on a low-iodine diet decreases the collection of I^{131} by the thyroid; but since PHP showed oestrogenic activity when tested by its effect on the uterine weight of immature rats, it was assumed that the effect of PHP on the thyroid collection of I^{131} was due to its oestrogenic activity. An alternate explanation is that the effect was indirect and produced through the secretion of the adrenal steroids, as judged by the enlargement of the adrenals of rats treated with PHP. According to Schaffenburg et al. (1951) the so-called pituitary inhibition of PHP may be considered as depending on the toxicity of the substance, which may give rise to a hormonal »shift« by means of the adaptation mechanism described by Selye (1946).

Difference of opinion also exists as to the value of PHP in alleviating the symptoms of Graves’ disease, for though Perrault’s favorable reports were confirmed by some authors
especially as regards a decrease in exophthalmos (Mahaux, 1950; Guinet, 1950; de Gennes et al., 1950; Olmer et al., 1950; Husslein, 1951; Sivadon et al., 1952), others were not able to do so. Thus de Gennes et al., who noted relief of exophthalmos and BMR in one case (de Gennes et al., 1950), found negative results in another (de Gennes et al., 1951). Di Ferrante & Zilli (1951) administered PHP to three patients suffering from Graves’ disease, but no significant change in pulse rate, goiter, BMR and blood cholesterol occurred. Schaffenburg et al. (1951) obtained no difference in the degree of exophthalmos and in the urinary gonadotrophins in two patients with Graves’ disease receiving PHP (BMR was normal at the time of treatment).

Our present work, an extension of a partial preliminary report (Iacono & Iannaccone, 1951), deals with the use of PHP in five cases of Graves’ disease.

MATERIAL AND METHODS

The diagnosis of Graves’ disease was well established in all of the patients both by clinical and laboratory means. All of them showed unmistakable signs and symptoms such as marked exophthalmos, diffuse goiter, increased pulse rate, tremor, nervous irritability and loss of weight; all had increased basal metabolic rates, and high plasma protein-bound iodine.

PHP was given by mouth during meals in the form of tablets in daily, divided doses ranging from gm. 0.5 to gm. 2.0 per day, for 45 to 80 days.*) Even when the dose was large, no untoward effects were noted. Only in one patient were there occasional and not very marked complaints of gastric hyperchlorhydria; following our suggestion, keratin-coated tablets were then made available for this subject and were always well tolerated.

*) p-hydroxypropiophenone used in this study was supplied by Recordati, S. A., Correggio, Italy.
Changes in exophthalmos (judged by inspection), goiter, tremor, pulse rate, blood pressure, body weight, basal metabolic rate (BMR), specific dynamic action of proteins (SDA), and plasma protein-bound iodine (PBI) were recorded periodically throughout the period of treatment.

SDA was determined by the following method. BMR was established by the usual technique. On the same day a meal consisting of 200 gm. of broiled chopped beef was given. The metabolic rate was again determined one hour, two hours and three hours after the meal and the highest percentage increase over the basal metabolism was calculated.

Determination of PBI was performed by an adaptation of the method of Connor et al. (1949) (normal range from 3.7 to 6.7 gamma per cent).

RESULTS

Exophthalmos, goiter and tremor were not affected by treatment with PHP in any of the cases. Other variations during the course of treatment are summarized in Table 1.

The findings show that neither clinical signs nor BMR, SDA, PBI were significantly improved by the treatment, even when patients were receiving high doses of PHP. An amelioration of exophthalmos, goiter, pulse rate, SDA and PBI resulted initially in one case (case 5), but was only transient as proved by subsequent course.

COMMENT

The above mentioned animal experiments offer evidence against the hypothesis that PHP inhibits TSH. However, should this hypothesis be proved to be correct, one is not forced to conclude that PHP may be useful in the therapy of Graves' disease, since in the blood of hyperthyroid subjects the TSH concentrations have usually been found to be in the normal range, thus indicating that hyperplasia and overactivity of the thyroid gland in such patients cannot be definitely
Table 1.

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Duration of Graves' disease prior to treatment</th>
<th>Dose of PHP, ml. daily</th>
<th>Duration of treatment, days</th>
<th>Pulse rate</th>
<th>Blood pressure, mm. Hg.</th>
<th>Body weight, Kg.</th>
<th>BMR per cent</th>
<th>1st hr.</th>
<th>2nd hr.</th>
<th>3rd hr.</th>
<th>Highest percentage increase</th>
<th>PBI gamma per cent</th>
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<td>1.</td>
<td>G.</td>
<td>M</td>
<td>36</td>
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<td>20</td>
<td>140/65</td>
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<td>+80</td>
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<td>+90</td>
<td>+86</td>
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<td>O</td>
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<td>108</td>
<td>155/95</td>
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<td>0</td>
<td>98</td>
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<td>C</td>
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<td>+47</td>
<td>+77</td>
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</table>

The figures representing the highest percentage increase over the basal metabolism are derived according to *Fulton & Cushing* (1932), by dividing the highest increase in metabolism by the basal metabolism. Thus, in patient No. 1, BMR was 176 per cent of normal; the highest metabolism reached following the test meal was 194 per cent of normal; the highest percentage increase is therefore (194—176)/176 or 10 per cent.
referred to abnormally high TSH concentration in the blood (D'Angelo et al., 1951). Moreover Perrault's assumption that exophthalmos in Graves' disease is related to high TSH titers in the blood and hence that its amelioration after treatment with PHP proves that PHP inhibits TSH, hardly seems likely, inasmuch as exophthalmos was found to be present when TSH was absent, normal, or excessively high in the blood, and to be absent in patients with high TSH levels (acromegaly, hypothyroidism) (D'Angelo et al., 1951). Thus, the rationale of administration of PHP in Graves' disease is open to objections and in fact negative results were previously reported (de Genès et al., 1951; Di Ferrante & Zilli, 1951; Schaffenburg et al., 1951).

Our own experience confirms that exophthalmos, goiter, pulse rate and BMR are not alleviated by PHP and, in addition, shows that SDA is not significantly changed and PBI does not reach a normal level after treatment with PHP.

The specific dynamic action of proteins is still a controversial phenomenon and its relationship with the thyroid-pituitary axis is not at present clear (Wilhelmj, 1935; Schaffer & Le Breton, 1938; Barker, 1949). SDA was found within the normal limits by Du Bois (1916) in exophthalmic goiter, by Fulton & Cushing (1932) and Johnston (1932) in cases of acromegaly and pituitary tumors, by Gaebler (1929) and by Artundo (1931) in dogs after removal of the hypophysis. On the other hand, Plaut (1922) and Liebesny (1924) noted an increased SDA in acromegaly; Plaut (1922), Liebesny (1924) and Goldzieher & Gordon (1933) emphasized the occurrence of definitely decreased SDA in the vast majority of hypopituitary cases; Liebesny (1924) and Houssay (1934) observed an increase in SDA following the administration of anterior pituitary extract; Löw & Krüma (1937) suggested that SDA results from stimulation of the hypophysis-diencephalon system by the exogenous aminoacids in the blood; and recently White et al. (1947) postulated an anterior pituitary substance which increases oxygen consumption other than through the mediation of the thyroid. Therefore, although many factors beside
the hypophysis are able to influence SDA, it seems that changes of SDA, when added to other clinical and laboratory findings, may be indicative of pituitary function. However, no significant difference in SDA occurred in our patients following the administration of PHP.

As regards PBI, Rapport & Curtis (1950) have recently summarized the evidence in favor of the concept that PBI is, at least in part, thyroxine or thyroxine-like; thus, it appears to be an index of the circulating thyroid hormone and to offer the most accurate measure of the activity of the thyroid gland. Taking into account that TSH is concerned with both the rate of formation of thyroxine (Morton et al., 1942) and the rate at which the thyroid hormone is released into the blood stream (Taurog et al., 1946), and since PBI has also been shown to decrease after hypophysectomy (Taurog et al., 1946) and to increase following the administration of TSH (Chaikoff et al., 1947), a decrease of PBI after the administration of a TSH-inhibiting substance would be expected, but this was not produced by PHP in our cases.

Although a definite decision cannot be arrived at without further work, it does not appear at present that PHP is able to improve the clinical and metabolic features in Graves' disease.

SUMMARY

Five patients with Graves' disease were given p-hydroxypropiophenone in daily doses ranging from gm. 0.5 to gm. 2.0 per day, for 45 to 80 days. Changes in exophthalmos, goiter, tremor, pulse rate, blood pressure, body weight, basal metabolic rate, specific dynamic action of proteins and plasma protein-bound iodine were recorded periodically throughout the time of treatment, but no significant variations occurred.
REFERENCES

Goldzieher, M. A. & Gordon, M. B.: Endocrinology 17, 569, 1933.
Houssay, B. A.: Endocrinology 18, 409, 1934.