appreciable fraction of the receptors and thereby protected them from combination with dibenamine and consequent blockade. "From results such as these it is concluded that epinephrine, noropinephrine and isopropylarterenol react with the same set of contraction receptors in the aortic smooth muscle."

This method has since re-appeared periodically as a tool for demonstrating that two drugs act on the same receptor. Pharmacologically, however, the basis of the method is not sound. The purpose of this communication is to point this out and demonstrate why. Two pharmacological concepts are involved here. (1) There is no *a priori* reason (as Furchgott himself points out) to suppose that any drug combines with only one site. Usually this appears to be the case in practice since the concentration is kept low so as to produce a pharmacologically effective drug-receptor combination only at the most sensitive site(s). But in the cross-protection method a large dose of the protecting agent is used so it is to be expected that an appreciable occupancy of many sites will result. (2) There is considerable evidence that stimulant drugs can stimulate a tissue markedly when only a small proportion of the receptors involved are free. (Whether this be pictured as 'spare-receptors' or 'spare-receptor capacity'² is immaterial here.) Consideration of these two concepts shows that the original conclusion is not unique. As an example let us consider a given receptor pool. We may picture a drug which (in the usual pharmacological concentrations) combines negligibly with it. However, at the much higher doses generally used for protection, this drug might occupy and protect say 5 per cent of receptors. This number of receptors would probably be quite sufficient for the production of a strong effect by a second drug (which is characteristically a strong agonist). Thus two drugs would appear to 'react with the same set of receptors', but the interaction would be of little or no pharmacological or physiological significance.

The converse conclusion, that is, that absence of protection is evidence that the two receptors are different, is also not rigorous. This is especially true if the stimulant drugs behave as Paton³ has suggested, that is, that their drug-receptor interaction is associated with a high turnover-rate. The blocking agent could then have access to all the receptors even during a relatively short exposure and the degree of protection could be negligible.

The method of 'cross-protection' seems therefore to be rather less useful than is generally recognized.

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PATHOLOGY

Effect of Thiouracil on the Development of Mammary Tumours in Rats Induced with 9,10-Dimethyl-1,2-Benzanthracene

THE induction of mammary tumours in rats by the oral feeding of a chemical carcinogen has been found to depend on the hormonal state of the animal¹⁻³. This communication deals with the attempted production of such mammary tumours by the oral administration of 9,10-dimethyl-1,2-benzanthracene

Table 1. SUMMARY OF METHODS AND GROUPS			
No. of rats	PTU		DMBA
	5 mg daily for 95 days		10 mg once/week. Reduced to 5 mg after 4 weeks. Stopped at 95 days
30	None		As above
30	5 mg daily for 95 days		None

Table 2. MAMMARY GLAND TUMOUR INCIDENCE IN RATS GIVEN DMBA AND DMBA + PTU

Days after first administration of			
	DMBA	80	100
Rats with tumours	DMBA	10/24	16/22
	PTU + DMBA	1/22	4/21
P*		0.003421	0.000503

* P was calculated by the method of Yates and Fisher (see *Statistical Methods for Research Workers*, Fisher, R. A., thirteenth ed., 96 (1958)).

(DMBA) in rats made hypothyroid with propylthiouracil (PTU).

Non-inbred rats descended from stock imported from Sprague-Dawley of Madison, Wisconsin, and commercially available in Britain were bought at 40 days of age. After a formal randomization process they were divided into groups for treatment as shown in Table 1.

10 mg DMBA, dissolved in 0.5 ml. corn oil, was given by gastric tube once weekly, the first dose at 50 days of age. 5 mg PTU, suspended in 0.5 ml. of sterilized arachis oil, was given by mouth daily from 50 days of age.

Of the group given PTU + DMBA mammary gland tumours were found in 1 of 22 rats alive at 60 days, 4 of 21 rats at 80 days and in 7 of the surviving 14 rats at 100 days (Table 2). Corresponding figures for DMBA alone were 10 rats with tumours of 24 alive after 60 days, 16 of 22 rats at 80 days and 20 rats with tumours of 20 after 100 days. The difference in the numerical incidence of mammary tumours between rats having DMBA + PTU and rats having DMBA alone is highly significant statistically ($P < 0.01$). Mammary gland tumours were not seen in any rat given only PTU. The mortality of the rats given PTU + DMBA was somewhat higher than that of the rats given only DMBA.

Jull and Huggins² showed that after DMBA, fewer rats developed mammary tumours in thyroidectomized animals than in intact controls. Our results indicate that hypothyroidism chemically induced by PTU is capable of producing the same effect. Jull and Huggins have suggested that this might be the result of diminished caloric intake.

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² Jull, J. W., and Huggins, C., *Nature*, **188**, 73 (1960).

³ Young, S., *Nature*, **190**, 356 (1961).

Uptake of Proteins by Malignant Cells

A RECENT immunohistochemical investigation of p-dimethylaminoazobenzene-induced hepatomas in rats¹ has supported the view that plasma proteins can be taken up by cancer cells without prior extracellular hydrolysis². However, hepatic parenchymal cells after only minor injury are known to be permeable to serum proteins³. We have therefore studied by direct and indirect fluorescent tracing methods⁴ the uptake of serum proteins in tumours arising in other tissues.