fatty change[5], from necrosis[6] and from the excessive accumulation of iron[7] so it would appear now that primary liver cancer, at least in the rat, can also be dissociated from observable necrosis, fibrosis and bile duct hyperplasia. In this connection it should be mentioned that LAWS *et al.*[8] found that, after feeding aceto-aminofluorene the neoplastic transformation in ZYMBAL'S gland arose from tubules which did not show any antecedent cystic or other pathological change, such as occurs commonly in the liver before the emergence of cancer. It may be too early to assert that the extensive liver disease, accompanied by cirrhosis, commonly seen in the African throughout the Continent of Africa may not necessarily predispose to liver cancer.

Since a malignant neoplasm arising from the epithelium of a respiratory bronchiole and different from that commonly seen in adenosis of the lung was also encountered in one of the rats affected also with liver cancer, it is not unlikely that progesterone and testosterone propionate may be able to induce carcinoma in organs other than the lung and the liver. If the findings can be confirmed in a larger series of rats now under investigation in our laboratory, a different orientation may be given to the attack on the etiology of primary carcinoma of the liver in man.

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Résumé

Le carcinome hépatocellulaire du type trabéculaire a paru dans 2 rats sur 5, 745 jours après l'implantation de boulettes de progestérone cristallin et de propionate de testostérone, pesant 8 à 10 mg chacune. Un de ces rats a développé un carcinome provenant de l'épithélium d'une bronchiole respiratoire. L'absence d'une cholangiofibrosite antécédente, d'une nécrose ou d'une cirrhose hors de l'endroit de la tumeur du foie chez les rats soumis aux épreuves expérimentales, peut nécessiter un nouvel examen de la signification des lésions hépatiques comme facteur prédisposant au cancer chez l'homme.

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From Parasympathomimetics to Parasympatholytics by Homologous Substitution

The effect of a drug on a biological object is the result of the interaction of drug molecules with receptors.

The activity of a drug is determined by the affinity and the intrinsic activity[1]. The affinity is the equilibrium constant for the interaction of the drug with the receptors, which is in the simplest case equal to the reciprocal of the dissociation constant of the drug-receptor complex. The intrinsic activity (i.a.) is the effect per unit of drug-receptor complex. Drugs with a high intrinsic activity on parasympathetic receptors are pure parasympathomimetics, those with an intrinsic activity zero, are competitive antagonists of the mimetics. Drugs with an intermediate intrinsic activity behave as parasympathomimetics or -lytics, depending on the state of the receptor system. Parasympathomimetics and -lytics have affinity to the same receptor system.

In a physico-chemical sense the reaction between drug and receptor implies an interaction between the electrical fields inherent to their charge-distributions. Not only the field inherent to the kationic and anionic sites and other regions with a high or low electron density, but also those which underly the Van der Waals forces and hydrogen bonds have to be taken into consideration. The affinity is coherent with the interaction between the fields in the most general sense. The intrinsic activity often will be connected with a special part of this interaction.

Two magnitudes are of special importance for the drug-receptor interaction and its biological effect: (a) the charge-distribution on drug and receptors, (b) the sterical configuration of drug and receptor as far as they interfere with the interaction between the fields. Little is known about the molecular properties of the receptors. Of the drug-molecules the chemical structure and certain physico-chemical properties are known.

The study of pharmacodynamics has to be based on the relation between the properties of the drug and the effect. On the basis of the results thus obtained conclusions may possibly be drawn about the properties of the receptors. Evidence is accumulating in the literature[2] that in homologous series of drugs a change in the structure is often combined with a gradual change in the affinity. In an analogous way the intrinsic activity may be expected to change gradually with the structure.

Most parasympathomimetics contain in their configuration a positive and a negative grouping, located on a certain distance[3].

The same holds for the -lytics. This indicates that these groupings are important for the affinity to the parasympathetic receptors. In contrast with the -mimetics, the -lytics have large groups on the 'negative' side of the molecule[4]. With respect to substitution on the positive side of cholinergic drugs, e.g. succinylcholine tested on the myoneural junction, it was found that successive replacing of methyl groups by ethyl groups resulted in a gradual change from mimetic to lytic[5]. On the basis of the considerations given before it may be expected that homologous substitution on the positive, R_3, or on the negative side, R', of the dioxolane compound 2249 F (dilvasène)[6], will result in a gradual change of the

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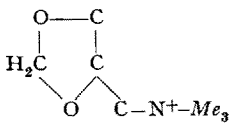
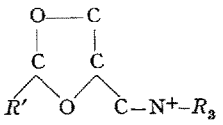
parasympathomimetic via drugs with a dual mode of action into parasympatholytics.



2249 F; H–F–Me_3



R'–F–R_3

1. *Substitution on the 'Negative Side'.*—One hydrogen atom is replaced by an alkyl group increasing in length. It may be expected for this R'–F–Me_3 series that, starting with H–F–Me_3, the intrinsic activity decreases, so that finally parasympatholytics are obtained. The expectation was confirmed by experiments using the rat jejunum as a test object. The drugs H–F–Me_3, *Me*–F–Me_3, and Et–F–Me_3 are parasympathomimetics (high i.a.). Bu–F–Me_3 and Hex–F–Me_3 are parasympatholytics (i.a. is zero). (They behave as competitive antagonists of the mimetics Fig. 1). Pr–F–Me_3 with its intermediate intrinsic activity is a drug with a dualism in action. Thus Pr–F–Me_3 behaves as a parasympathomimetic or as a -lytic, dependent on the state of the receptor system (Fig. 2). As may be seen from the table, for all R'–F–R_3 compounds elongation of the alkyl chain R' results in a decrease of the intrinsic activity.

On the same basis in the R_2'–F–R_3 series a continuous change from parasympathomimetics into -lytics may be expected. The experimental confirmation is summarized in the table.

'Intrinsic activities' (i.a.) and log 'affinities'* (aff.)

R'	R_3							
	Me_3		Me_2Et		$MeEt_2$		Et_3	
	i.a.	aff.	i.a.	aff.	i.a.	aff.	i.a.	aff.
R'-F-R_3 compounds								
H	1	5·3	1	4·8	0·4	3·6	0·2	3·5
Me	1	7·3	1	7·1	0·3	4·0	0	3·6
Et	1	5·4	0·5	5·0	0	4·6	0	4·2
Pr	0·5	4·9	0	4·9	–	–	0	4·7
Bu	0	4·8	–	–	–	–	–	–
Hex	0	4·7	–	–	–	–	–	–
R_2'	R_2'-F-R_3 compounds							
Me_2	1	4·9	0·6	4·8	0·2	4·3	0	4·3
Et_2	0·5	4·6	0	4·8	–	–	–	–
Pr_2	0	6·4	0	6·6	–	–	–	–
R'	R'-N^+-R_3 compounds							
Bu	1	5·2	0·5	5·1	0	4·0	0	4·3
Pent	1	5·4	0·4	5·2	–	–	0	4·4
Hex	0·9	5·0	0·1	4·7	–	–	0	5·0
Hept	0·1	4·6	0	5·1	–	–	0	5·5
Oct	0	5·0	–	–	–	–	0	5·4
Non	0	5·0	–	–	–	–	0	5·6
Dec	0	5·9	–	–	–	–	0	–
Dodec	0	6·0	–	–	–	–	–	–

acetylcholine: i.a. = 1, aff. 7·0; atropine: i.a. = 0, aff. 8·7

* The log affinity is the pD_2 value for the mimetics and the pA_2 value for the lytics.

2. *Substitution on the 'Positive Side'.*—The methyl groups on the quaternary N-atom are replaced successively by ethyl groups. It may be expected that starting with the parasympathomimetic *Me*–F–Me_3, the intrinsic activity decreases, so that here also parasympatholytics may be obtained in the end. The experiments confirmed the expectations. Thus it was found that *Me*–F–Me_3 and *Me*–F–Me_2 Et are parasympathomimetics (high i.a.), *Me*–F–Et_3 is a -lytic (i.a. is zero).

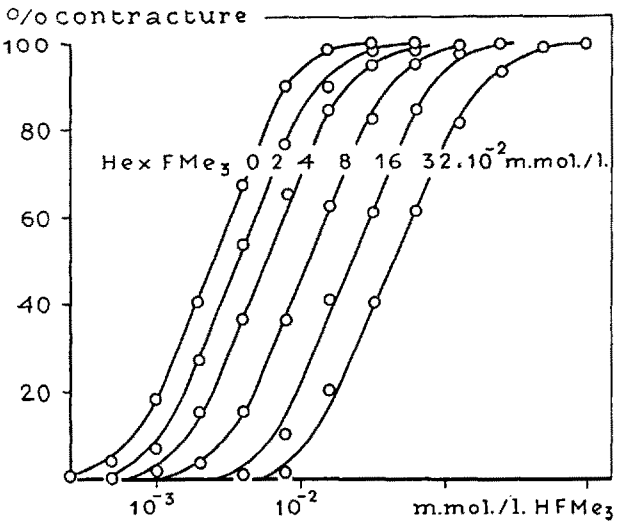


Fig. 1.—Cumulative log dose-response curves on the isolated rat jejunum for H–F–Me_3 in the presence of constant concentrations of the competitive antagonist Hex–F–Me_3.

Me–F–*Me*Et_2 is a drug with dualism in action (intermediate i.a.). (See the table.) Successive substitution on the positive side alone is sufficient to change the R'–F–R_3 compounds from parasympathomimetics into -lytics.

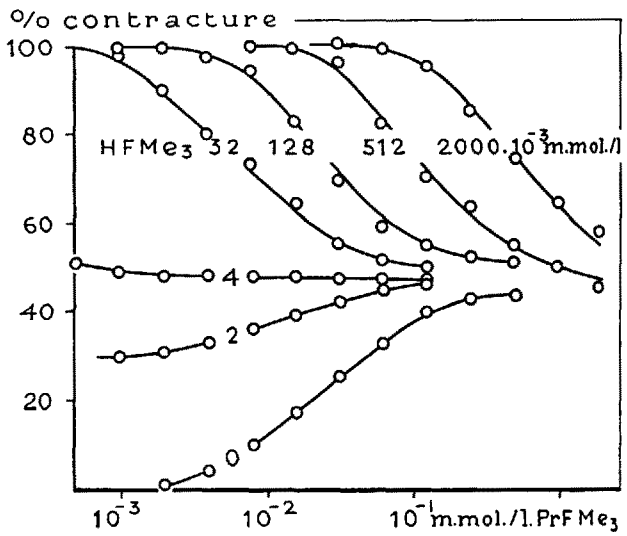


Fig. 2.—Cumulative log dose-response curves on the isolated rat jejunum for Pr–F–Me_3 in the presence of constant concentrations of H–F–Me_3. Dependent on the response already given with H-F-Me_3, Pr–F–Me_3 is synergistic, inactive or antagonistic with respect to H–F–Me_3. Independent of the initial response for high values of Pr–F–Me_3 the same response is always obtained.

Substitution of larger groups on the 'positive' as well as on the 'negative' side results in a change of -mimetic

into -lytic. From a combination of both types of substitution, a more pronounced decrease of the intrinsic activity can be expected. This was confirmed by the experiments. In this way in the various homologous series, the intrinsic activity reached zero for Bu–F–Me_3, Pr–F–Me_2Et, Et–F–MeEt$_2$ and Me–F–Et$_3$ (see the table).

Not only for the intrinsic activity but also for the affinity, regular changes with the molecular structure were observed.

It was mentioned before that the charge distribution and the sterical configuration of the drug may be considered to be of special importance for the effect. For drugs with an affinity to cholinergic receptors the most pronounced electrical charge is found on the quaternary N^+-atom.

Ethylation, which means introduction of larger and electron-repulsing groups, results in a decrease of this positive charge. At the same time as a consequence of sterical hindrance, the influence of this charge on the field of the receptors is decreased. Possibly a kind of masking of the charge by ethyl groups may also be involved. From the experiments it may be concluded that there is a strong correlation between the molecular properties just mentioned and the intrinsic activity. With respect to the affinity, it was found that for the parasympathomimetics ethylation resulted in a decrease of the affinity, while for the -lytics no correlation was found.

Substitution on the negative side has hardly any influence on the charge of the quaternary N^+-atom. The decrease in the intrinsic activity caused by the elongation of R' probably has to be ascribed to a sterical interference with respect to the approach of the positive charge to the receptors. The negative grouping is not essential with respect to parasympathetic activity on the rat jejunum. This is clearly demonstrated by the results obtained with some series of homologous alkyltrialkylammonium compounds (R'-N^+-R_3), which closely resemble those obtained with the dioxolane compounds (see table).

Introducing affinity and intrinsic activity into the receptor theory, it was possible to predict biological properties for a large number of new dioxolane compounds and a series of alkyltrialkylammonium compounds.

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Pharmacological Institute, R. C. University of Nijmegen, Netherlands, December 29, 1956.

Zusammenfassung

Auf Grund der theoretischen Befunde war zu erwarten, dass Änderungen an der negativen und positiven Seite der Dioxolan-Verbindung 2249 F zu graduellen Übergängen von Parasympathikomimetika zu Parasympathikolytika führen würden. Die Experimente bestätigten die Erwartungen vollauf.

Untersuchung homologer Reihen von Alkyltrialkylammonium-Verbindungen zeigte die negative Gruppe als nicht wesentlich für die parasympathische Wirkung und ergab ebenso einen graduellen Übergang von Mimetika zu Lytika.

Einfluss von Isonikotinsäurehydraziden auf den Verlauf der Körpertemperatur nach Reserpin, Monoaminen und Chlorpromazin

Reserpin, das bei Kaninchen Sedation und Miosis verursacht, bewirkt nach Vorbehandlung mit Isopropylisonikotinsäurehydrazid (Iproniazid, *Marsilid*) Exzitation, Mydriasis und Pilo-Erektion, ähnlich wie Lysergsäurediäthylamid (LSD)[1]. Reserpin setzt gewebegebundenes 5-Hydroxytryptamin (5HT) und Catecholamine in Gehirn und anderen Organen frei[2]. Diese Amine werden zum Teil durch Wirkung von Monoaminoxydase inaktiviert, einem Ferment, das durch Iproniazid und in viel schwächerem Masse durch Isonikotinsäurehydrazid (Isoniazid, *Rimiform*) gehemmt wird[3]. Die Abbauhemmung der infolge Reserpin-Wirkung freigesetzten Monoamine durch Iproniazid führt möglicherweise zu unphysiologisch hoher Konzentration von freien Monoaminen im Gehirn. Diese Hypothese könnte den LSD-artigen Effekt von Reserpin nach Iproniazid-Vorbehandlung erklären[4].

In der vorliegenden Arbeit sollte die Bedeutung der Monoaminoxydase bei der Wirkung von Reserpin und einigen Monoaminen weiter abgeklärt werden. Dazu wurde der Einfluss von Iproniazid und Isoniazid auf die Temperaturwirkung von Reserpin und verschiedenen Monoaminen bei Kaninchen untersucht und mit LSD sowie Chlorpromazin verglichen. Chlorpromazin setzt im Gegensatz zu Reserpin kein 5HT frei[5].

Methodik. Bei Kaninchen wurde 24 h nach Iproniazid-Behandlung bzw. ohne Vorbehandlung Reserpin, 5HT, Adrenalin, Tyramin, Phenyläthylamin, Mezcalin und Chlorpromazin injiziert. Weitere Tiere erhielten 24 h nach Isoniazidinjektion Reserpin und 5HT, sowie LSD ohne Vorbehandlung. Die rektale Temperatur wurde mit Thermoelementen zweimal vor und achtmal nach Verabreichung von Reserpin, Chlorpromazin und der Amine halbstündlich gemessen[6].

Resultate.

a) 0,5 und 1 mg/kg Reserpin intravenös erzeugten bei Kaninchen Hypothermie, während LSD hypertherm

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