

are treated with reserpine and then given amphetamine (19, 20).

The data presented here on the effect of PCPA treatment in cats represent minimum estimates of change. They include only positive identification of behavior patterns made during relatively short—although daily—observation periods. They are sufficient, however, to show that long-term administration of PCPA has a pronounced and encompassing effect and to suggest that serotonin may have a pervasive role in regulating drive and behavior in the cat.

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References and Notes

- Ordinarily we did not allow cats to interact during experiments in order to minimize the possibility of a cat fight with damage to a valuable animal or its implanted electrodes. Thus it would have been possible to complete a whole study without seeing two cats interact in the suggestive manner described here. In this particular instance, the cat treated with PCPA was brought into the recording room while another cat was still out of his recording cage receiving wound care and temperature measurement. The cat treated with PCPA leaped out of the experimenter's arms and was instantly upon the other male cat in a typical feline sexual mount.
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- The male-male interaction was used as a measure of hypersexuality because of the marked proclivity of normal male cats to mate with estrous females. When PCPA-treated animals were presented with such a female, they exhibited no hesitation in attempting a mount.
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- Three of the 26 cats were killed after 5 days of PCPA treatment and another four died during the course of the experiments from causes unrelated to the experimental manipulation. Of the remaining animals, six were killed after nine or more days of treatment; and five died from presumed toxic effects of the drug, thus leaving eight for observations during the recovery period.
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Brain Norepinephrine: Enhanced Turnover after Rubidium Treatment

Abstract. After biosynthesis of norepinephrine was inhibited, treatment of rats for 10 days with rubidium chloride (0.6 milliequivalent per kilogram of body weight) caused an increase in the rate of disappearance of norepinephrine in the brainstem but not in the telencephalon. Also the utilization of intracisternally injected tritiated norepinephrine was increased and was accompanied by a shift in the pattern of norepinephrine metabolism to normetanephrine. These data suggest that greater amounts of neuronally stored norepinephrine were released to central adrenergic receptors.

The action of rubidium on central excitability in monkeys has been described (1). The effectiveness of another alkaline earth cation, lithium, in the treatment of mania has been tentatively associated with the effect of this ion on brain amine metabolism (2) which is perhaps related to an interaction with other cations intimately involved in adrenergic neurotransmission. In contrast to the effects of lithium in both humans and infrahuman species, rubidium causes hyperactivity, increased aggressiveness, and electroencephalographic activation. We examined the effects of short-term rubidium treatment on gross behavior and on the metabolism of brain catecholamines in rats.

Our experiments were performed on male Long-Evans rats that weighed 250 to 300 g at the start of the study. The rats, housed in groups of four, were injected daily with saline or with rubidium chloride (0.6 meq per kilogram of body weight; intraperitoneally) for ten consecutive days. Twenty-four hours after the last injection, groups ($n=16$) of both the control rats and those treated with rubidium were in-

jected with 200 mg/kg (intraperitoneally) of the methyl ester of DL- α -methyl-*p*-tyrosine (α MT), an inhibitor of catecholamine biosynthesis which can be used to measure the rate of utilization of catecholamines (3). Animals were killed at intervals thereafter.

Brains were dissected into stem (comprising diencephalon, metencephalon, and myelencephalon) and telencephalon fractions for amine determination. After the fractions were homogenized in 0.4N perchloric acid, the supernatants were adjusted to pH 6.5 and passed over IRC-50 resin. Norepinephrine (NE), dopamine (DA), and 5-hydroxytryptamine (serotonin, 5-HT) were assayed spectrophotofluorimetrically after elution from the resin by 0.5N acetic acid. Values for brain NE and DA concentrations were subjected to regression analysis by least-square fitting to obtain rate constants for their disappearance after inhibition of catecholamine biosynthesis.

In a second experiment, control rats and those treated with rubidium were given an intracisternal injection of [3 H]NE (8.3 μ c; specific activity, 7 c/mmole; New England Nuclear).

Groups of six control and rubidium-treated rats were killed from 6 minutes to 6 hours later. Whole brains were assayed for NE and its metabolites by the procedure of Schanberg *et al.* (2) by chromatography on alumina and Dowex 50W-X8 columns before liquid scintillation spectrophotometry.

There were no differences in the growth rate of the two groups of rats over the 10-day treatment period. The behavior of the rats treated with rubidium was not noticeably different from that of the control animals when compared within their home cages. Upon handling, however, the treated rats became extremely irritable, displaying marked vocalization and aggressiveness toward the handler, particularly during the last 3 days of treatment.

Initial concentrations of 5-HT, DA, and NE were not altered significantly by rubidium treatment, although NE concentrations in the brainstem of the rats treated with rubidium tended to be higher than that in controls (rubidium, 0.633 ± 0.025 $\mu\text{g/g}$; control, 0.580 ± 0.022 $\mu\text{g/g}$; $.10 > P > .05$). Rate constants for the decline of whole brain DA and telencephalic NE after treatment with αMT were nearly identical in both groups. Likewise, calculated utilization rates and half-lives were not altered by drug treatment. On the other hand, brain stem NE in the rats treated with rubidium disappeared at a significantly faster rate than in the control animals (Table 1).

The utilization rate of NE is increased in the brainstem, but not in the telencephalon, by rubidium treatment. Previous studies with psychoactive drugs as well as with lithium have demonstrated that an increase in the rate of metabolism, as measured by αMT , may not be synonymous with an enhanced release of the "physiologically active" NE onto appropriate brain receptors. Thus, amphetamine, an antidepressant, increased normetanephrine formation, while lithium, which is used to control mania, decreased the normetanephrine concentrations by increasing the intraneuronal metabolism of NE; both agents resulted in an increased rate of utilization (2, 4). To further evaluate the changes induced by rubidium, the rate of utilization and the metabolic fate of intracisternally administered [^3H]NE was determined in the two groups of rats.

Six minutes after the intracisternal injection, both groups of rats had similar absolute amounts of labeled NE in brain (Fig. 1), an indication that

Table 1. Kinetic data on norepinephrine in the brainstem of rats treated with DL- α -methyltyrosine methyl ester (200 mg/kg) after treatment with saline or with rubidium chloride (0.6 meq/kg) for ten consecutive days. The results are expressed as the mean \pm standard deviation.

Rate constant k (hr^{-1})	Utilization rate* kC_0 ($\mu\text{g g}^{-1} \text{hr}^{-1}$)	Half-life (hr)
<i>Treatment with saline</i>		
0.22 ± 0.04	0.13 ± 0.03	3.18 ± 0.42
<i>Treatment with rubidium</i>		
$0.29 \pm 0.03^\dagger$	$0.18 \pm 0.02^\dagger$	$2.42 \pm 0.24^\dagger$

* Product of the rate constant and the basal concentration (C_0) of NE. $^\dagger P < .05$.

rubidium treatment did not affect the accumulation in vivo of NE under the conditions used. The disappearance rate of labeled NE was increased by rubidium treatment. At the same time, concentrations of labeled normetanephrine increased up to fivefold in the rats treated with rubidium (that is, 53 ± 4 nc/g in rats given rubidium as opposed to 11 ± 1 nc/g in control rats 3 hours after administration of [^3H]NE; $P < .01$). The fraction containing the ^3H -labeled deaminated-*O*-methylated metabolites was unaltered. Thus, the disappearance rate of NE increased in rats treated with rubidium whether measured by αMT or by radiotracer methods. As shown in the second experiment, the increase in rate is accompanied by a shift in the metabolism of NE toward normetanephrine.

According to current models of

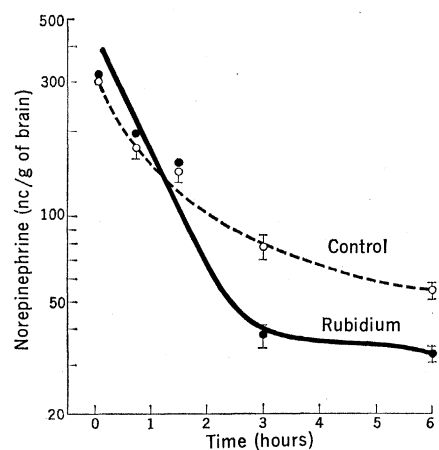


Fig. 1. Concentrations of [^3H]norepinephrine in whole brain after intracisternal injection of 8.3 μc of [^3H]NE in rats given short-term treatment with rubidium chloride or with saline. Each point represents the mean (\pm S.E.M.) from six animals. The values are expressed in nanocuries of radioactive NE (isolated by alumina chromatography) per gram of whole brain. Animals were killed at the indicated time after injection of the labeled amine.

adrenergic function, physiologically active NE is released into the synaptic cleft by neuronal impulses, thereby activating appropriate receptors. Termination of the activity of released NE depends on an active reconcentration of the amine by presynaptic nerve terminal membranes and by conversion to normetanephrine by the extracellular enzyme catechol-*O*-methyltransferase (E.C. 2.1.1.6). The increased normetanephrine concentrations in the rats treated with rubidium support the concept of increased release of physiologically active NE. Whether the neuronal membrane uptake system for NE is also affected is not clear, though the 6-minute time point (Fig. 1) and another report on an in vitro system (5) indicate that NE uptake was essentially unaffected.

Sodium and magnesium are important ions, respectively, for the neuronal uptake and for the granular storage mechanisms for NE (6). There is some evidence that lithium and sodium, both highly hydrated ions, may share a complementary action in various physiological systems. Less hydrated ions such as rubidium, cesium, and potassium may also be interchangeable (7). The contrasting effects of lithium and rubidium on catecholamine metabolism raises the question of whether the actions of these cations are in any way related to those of sodium and potassium.

Comparison of our results with rubidium to those with lithium on [^3H]NE metabolism shows that the two alkaline earth cations cause different effects on catecholamine metabolism. Lithium increases uptake of NE into synaptosomes (8) and increases the intraneuronal metabolism of NE, as reflected by a decrease in normetanephrine accompanied by an increase in both the deaminated and deaminated-methylated metabolite fractions. This spectrum of changes has been interpreted to reflect a decrease in the concentrations of active NE on the transneuronal receptors (2), but also may be an alternate mechanism controlling either intraneuronal or transneuronal processes in catecholamine-containing neurons (9). In most instances lithium treatment did not affect NE turnover, although some reports indicate that an increased turnover after treatment with this cation may be a reflection of the enhanced intraneuronal catabolism of NE (4). The contrasting effects of lithium and rubidium on NE metabolism suggests more detailed pharma-

ecological studies of rubidium and related cations, such as cesium, with possible evaluation for their use in depressive states.

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How Much Food from the Sea?

We have read with interest John H. Ryther's recent article "Photosynthesis and fish production in the sea" (1). Ryther's estimate of annual fish production (about 100 million tons) falls within the range (80 to 2000 million metric tons) estimated in the past few years by other scientists (2). It is, however, at the lower end of this range. The importance of his contribution must be viewed in the light of whether or not his work provides a better focus on the yield of fishes that may be anticipated from the world's ocean.

The technique used by Ryther and other scientists who have derived estimates based on the flow of material through the food chain involves three primary considerations: the amount of carbon fixed annually; the efficiency with which nature transfers material up through the food chain; and the trophic level selected for calculating fish production or yields. Apart from the uncertainty surrounding the total amount of oceanic carbon fixed, such estimates of potential fish production are based i) on the assumption that the complex and variable food web in the sea can be treated as a simple chain of trophic levels and that fish production can be assigned to a specific level in the chain, ii) on the belief that it is possible to deduce the variable values for efficiency of transfer of material from predator to prey to a single set of values representing ecological efficiency, and (iii) on a

guess as to the percentage of production at present available to man.

Estimates obtained by this technique are extremely sensitive to the values assigned these parameters. Ryther's table 1 (1) represents a matrix of ecological efficiency and trophic levels. The choice between two adjacent levels involves a possible error of an order of magnitude or more, depending on the ecological efficiency factor chosen. The choice within a given range of ecological efficiencies involves error factors ranging from approximately 2 to 15. Even when other sources of uncertainty are ignored, Ryther's estimates could easily be in error in either direction by a factor of 1 to 2 orders of magnitude.

The sensitivity of this technique for estimating fish production has been recognized by most workers who have used it. Ryther departs from his predecessors in that he categorizes the ocean into "provinces," using relative primary productivity as a criterion, and subsequently examines the potential fish harvests of these provinces. His relatively low figure for total potential production of fish results from his selection of the third and fifth trophic level in calculating fish production from the coastal and oceanic provinces, respectively, and from the small total area suggested for the upwelling province.

Ryther presents little explanation for his use of trophic levels three and five steps removed from primary production

for the coastal and ocean areas. We doubt that there are any plankton ecologists who would agree "that virtually all the copepods, many of which are themselves carnivores, must be preyed upon by chaetognaths," even in the open ocean. For fishes in general, Ryther follows the logic of other biologists who have based trophic levels on the feeding habits of adult forms only. In many species, including the tunas and dolphins, the greatest net growth of the population occurs during the early life history of the species. It is common for many species of fish to attain the maximum weight potential before the species reaches maturity and relatively early in its life span. In fact, for adults, the weight added to the population in any time period is often exceeded by losses due to natural mortality. Thus, adults degrade net productivity rather than add to it. Fishing normally will change the population structure toward smaller sizes which have a higher ecological efficiency and which feed on organisms lower in the food chain. At any rate, there is considerable evidence that some important pelagic fishes feed on invertebrates which are largely herbivorous. For example, over a great part of the eastern tropical Pacific the summer diet of adult yellowfin tunas (*Thunnus albacares*) is dominated by the herbivorous pelagic crabs *Pleuroncodes planipes* (3).

Also, the works of other authors suggest that the number of trophic levels proposed by Ryther may be too high. Blackburn (4) suggests two fewer links than Ryther does for the chain of trophic levels between phytoplankton and man in the open ocean environment of the tuna fisheries. Steele (5) has shown that the observed fish catches in the North Sea could be supported by primary production only if the fish were feeding mainly at the second trophic level (not at the third, as suggested by Ryther). Since Steele's paper was written, North Sea catches have been increased to over 3 million metric tons, in 1967 and 1968, or to more than 5 ton/km²—well above Ryther's estimate of total production.

On examining Ryther's table 3 (1), it becomes obvious that a small error in calculated productivity could make a considerable difference in the final estimates. For example, in recent work the English scientist Cushing (6) suggests a much greater size for the area of rich upwelling water than Ryther does. Ryther admits the possibility of error regarding this matter.