sition of storage products or actual growth.

The effect of varying temperatures on oxygen utilization was tested gasometrically. The euphausiids were found to have a Q_{10} of approximately 2 between 5° and 12°C. This would imply that when these animals cross the thermocline into warmer water their basal carbon needs increase. However, except those by Fox *et al.* (*7*), few published data exist on the amount of particulate carbon available for zooplankters in the sea.

Application of the method presented in this paper to other organisms, with proper attention to the experimental variables cited here, may permit a direct measurement of the carbon flow through biological systems in aquatic environments. Future investigations call for studies of relative nutritional states and comparative proportions of stored reserves in experimental animals (*8*).

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Toxicity of Bacterial Exotoxins by the Oral Route

Abstract. Reports to the contrary notwithstanding, both tetanus and diphtheria toxins are demonstrably orally toxic. The significance of this finding is considered in relation to the definition of those factors which are determinants of the potency of bacterial protein toxins by the oral route.

The statement has often been made that among the classical bacterial protein exotoxins, that is, diphtheria, tetanus, and botulinum, only the latter is poisonous by the oral route (*1*). Thus, it is tempting to attribute the orally toxic nature of botulinal toxin to characteristics unique to this toxin. Recently a different point of view has been evolving (*2*). Toxicity of proteins by the oral route can be conceived as resting on the fact that the intestinal barriers to systemic absorption are imperfect and permit the escape of small amounts of protein. If this hypothesis is correct, one might expect to find that in addition to botulinal toxin, other proteins which are poisonous in extremely small amounts are potentially oral poisons.

A logical candidate for a test of the concept is tetanus toxin, a simple protein, whose potency by parenteral routes is of the same order of magnitude as the type A botulinal toxin. We have, therefore, tested for the oral toxicity of tetanus toxin in spite of the negative reports in the bacteriological literature.

Employing the Namru strain of white mouse, three separately prepared batches of crude tetanus toxin, kindly supplied by a commercial source from production runs, proved to be orally toxic. A typical experience is recorded in Table 1. The specificity of deaths was confirmed by observation of the protective value of specific antitoxin. Repeated titrations showed that between 200,000 and 1,200,000 times the intraperitoneal LD_{50} was required for one oral LD_{50}. With the same strain of mice and crystalline type A botulinal toxin, 50,000 to 250,000 intraperitoneal LD_{50} are needed for an oral LD_{50} (*3*).

The tetanus toxin also proved capable of killing large guinea pigs (800 gm) when 600,000 or more intraperitoneal lethal doses were given an individual animal *per os*.

Tests were also performed with crude diphtheria toxin. An occasional Namru strain mouse was poisoned orally. The oral toxicity for guinea pigs was irregular in occurrence and required the use of volumes (>3 ml) of the toxic fluid near the practical limits for *per os* injections. Consequently, it did not prove practical to collect data for calculation of oral LD_{50} values. The sporadic nature of the observations of oral toxicity for the mouse by diphtheria toxin perhaps is not surprising, since mice are thousands of times less sensitive to the toxin parenterally than are guinea pigs (*4*). In the future it will be desirable to test more highly concentrated preparations of the diphtheria toxin than have been available for the present study: 6000 (crude toxin lot 65316 from Merck, Sharp and Dohme) and 30,000 (ultrafiltrate lot Rx 057435-437 Parke, Davis and Co.) intraperitoneal LD_{50} for the guinea pig per milliliter.

Can the reported lack of oral toxicity for tetanus and diphtheria toxins be reconciled with our positive findings? The answer may relate to the fact that unlike the situation for *Clostridium botulinum,* laboratory cultures of tetanus and diphtheria bacilli generally do not produce concentrations of toxin in a volume of fluid that is feasible to inject into the alimentary tract of small laboratory animals as a fatal single dose. In our experience with such material, a number of oral doses separated in time must be given in order to be able to introduce without regurgitation and loss of the injected preparation enough toxin for fatalities to occur. I believe that negative reports result from trials with single injections of insufficiently concentrated toxin. When concentrated toxin preparations are tried, I predict a much larger number of bacterial toxins than are presently known will prove to be orally toxic. In this event, the reputation of botulinal toxin as an oral poison must rest not on any single intrinsic property of the toxin molecule, but rather on the particular ecological circumstances which permit the presence, growth, and toxin production of *C. botulinum* in a variety

Table 1. Toxicity of tetanus toxin in mice of 18 to 20 gm weight by intraperitoneal and *per os* administration. The preparation employed was a crude culture filtrate kindly made available by a commercial source from a routine production run in which the Harvard strain of tetanus bacillus, grown in a protein digest medium, was used. The filtrate was potent enough to permit the oral introduction of a fatal dose in a volume of fluid well tolerated by the mouse. The technique of *per os* injection has been reported and does not result in macroscopic evidence of tissue trauma (*3*). With this preparation of toxin, 3 ml (but not less), when given orally to guinea pigs of 800 to 1000 gm weight, resulted in death. Eight control mice received 500 units of antitoxin and were then injected with 0.5 ml of undiluted toxin *per os*; none of these died.

Intraperitoneal		*per os*		
			Deaths/No. injected	
Dose and Dilution	Deaths/No. injected	Dose and Dilution	Mice not starved	Mice starved 18 hr
0.5 ml, 1×10^5	4/4	0.5 ml, undiluted	9/10	9/10
0.5 ml, 2×10^5	4/4	0.25 ml, undiluted	7/10	6/10
0.5 ml, 4×10^5	4/4	0.25 ml, 2-fold	2/10	2/10
0.5 ml, 8×10^5	0/4	0.25 ml, 4-fold	3/10	1/10
0.5 ml, 16×10^5	0/4	0.25 ml, 8-fold	1/10	1/10

of foods. One will also expect to find an occasional case of food poisoning when, by chance, a rare concatenation of events will result in significant production of toxin in foods by bacterial species not ordinarily considered food poisoning organisms (*5*).

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Effect of 5-Hydroxytryptamine and Iproniazid on Pregnancy

Abstract. The effects of 5-hydroxytryptamine and iproniazid on pregnancy in mice and rabbits were investigated. 5-Hydroxytryptamine can interrupt pregnancy at all stages in mice but is particularly effective early and late in pregnancy. Iproniazid exerts its action essentially in the first half of pregnancy. 5-Hydroxytryptamine produces striking hemorrhage in the placenta.

We were led to investigate the effects of 5-hydroxytryptamine (5-HT) and iproniazid on pregnancy, in view of the facts that (i) 5-HT is liberated in the body by reserpine (*1*), which has an effect on pregnancy in rats (*2*) and (ii) iproniazid inhibits the destruction of 5-HT by monoamine oxidase and is known to increase the level of 5-HT in rats (*3*).

Experiments were carried out on female mice of known fertility. The first day of pregnancy was counted from the finding of the vaginal plug. The animals were treated subcutaneously at various stages of pregnancy, since it had been shown previously that different drugs are effective at different stages (*4*). 5-Hydroxytryptamine was given in two divided doses per day, while iproniazid was given in a single daily dose. Treatment was given in the following periods: 1 to 6 days, covering the preimplantation zygotic development; 3 to 8 days, covering the period of implantation; 6 to 11 days, covering the early stages of decidua formation; and 11 to 16 days, covering the stage of well-developed placenta and well-differentiated fetus. The animals were observed for signs of vaginal bleeding and loss of weight. Laparotomy was performed on the day after the end of treatment. The results are shown in Table 1.

It is obvious that both drugs have effects on pregnancy though not exactly at the same stage. The effects of 5-HT appear to be most striking in the early and late stages of pregnancy, while iproniazid has marked effects in the first half of pregnancy, particularly at the period covering implantation, and little effect later on. The results suggest that one of the effects of both of these drugs is to prevent implantation.

The marked effects of 5-HT on established pregnancy led to a more detailed investigation at this stage, all experiments being performed on the 14th or 15th day. Animals were injected with total doses of 4, 2, 1, 0.375 to 0.5, and 0.15 to 0.24 mg of 5-HT given in divided injections spread over a period

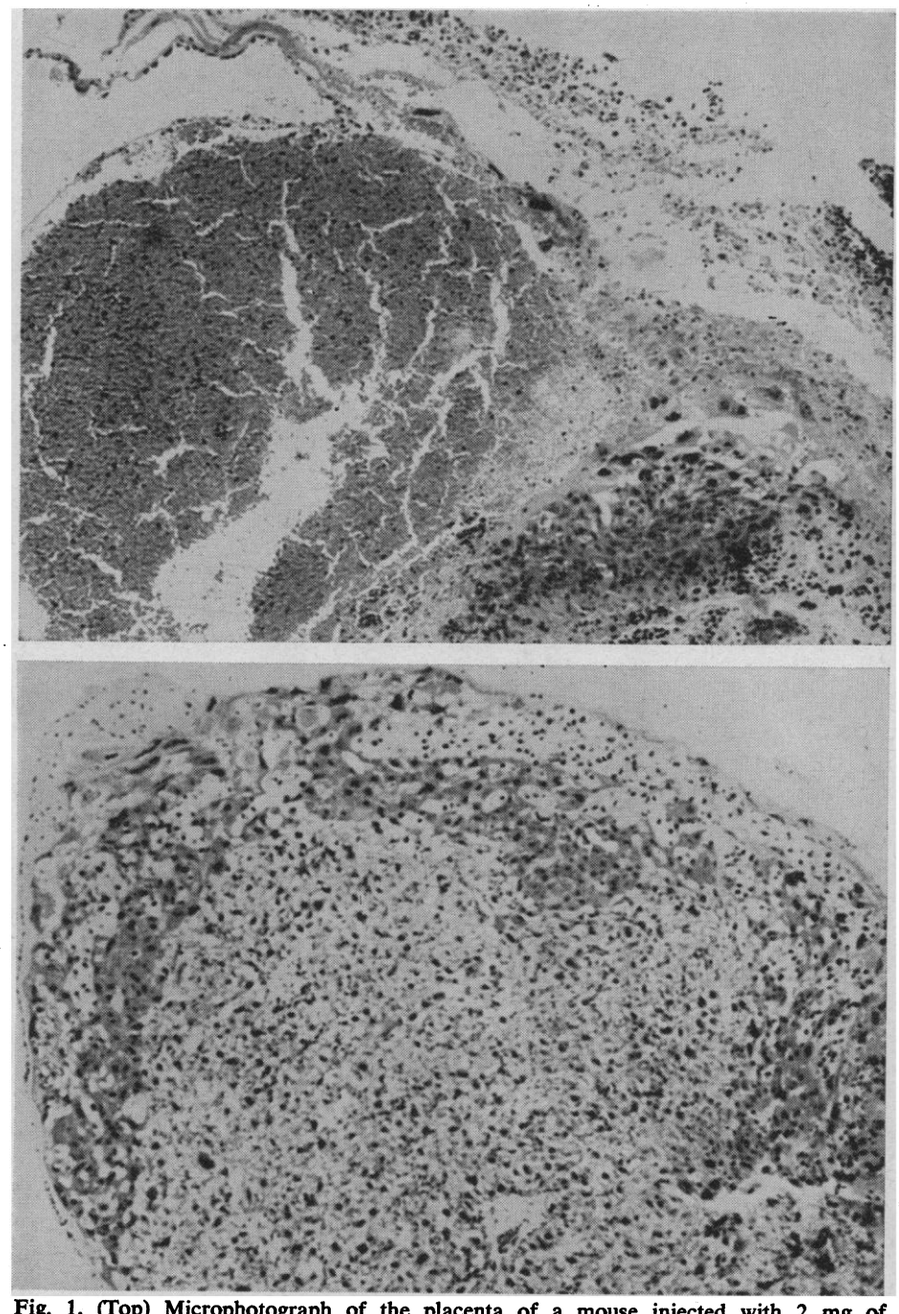

Fig. 1. (Top) Microphotograph of the placenta of a mouse injected with 2 mg of 5-HT (seven injections) on the 14th day of pregnancy and killed the next day. (Bottom) Normal placenta at the same stage of pregnancy. (About × 72.5)