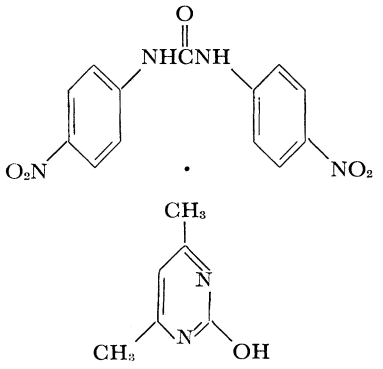
carbanilide (DNC) and 2-hydroxy-4,6-dimethylpyrimidine (HDP) was found to be among the most effective.

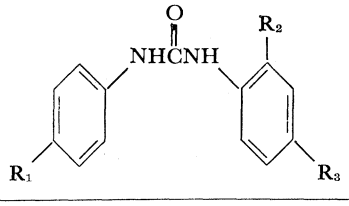


I

Some of the substituted carbanilides examined for anticoccidial activity are listed in Table 1. The compounds were mixed in the ration in concentrations of 0.01 percent or 0.1 percent and fed to young chicks at varying intervals before or after inoculation with oocysts of *Eimeria tenella*. Standardized procedures (*1*) were used throughout, and the criteria of anticoccidial effectiveness included survival rate, severity of lesions, inhibition of oocyst production, and relative weight gain. Based on all these criteria, the responses were classified as negative (0) to maximal (++++).

Under these conditions, the substituted carbanilide complexes varied from effective to ineffective. None of the complexing agents was active. Although DNC had definite anticoccidial activity when it was used alone, the potency was increased at least tenfold when it was complexed with HDP. No increase in anticoccidial activity was observed, however, on administration of a simple mixture of DNC and HDP. Similar studies with *E. acervulina* and *E. necatrix* in chicks and *E. meleagrimitis* and *E. gallopavonis* in poults have shown that the DNC · HDP complex effectively inhibited these species. Comparatively, the DNC · HDP complex is approximately fivefold more potent than nitrophenide (m,m′-dinitrophenyl-disulfide) in cecal coccidiosis.

Table 1. Anticoccidial response of substituted carbanilides.



R_1	R_2	R_3	Complexing agent	Dosage (% in feed)	Relative anticoccidial response
NO_2	H	NO_2	None	0.1	+
NO_2	H	NO_2	HDP	0.01	++++
NO_2	H	NO_2	AT	0.01	++++
NO_2	H	NO_2	PYR	0.01	+++
NO_2	CH_3	NO_2	HDP	0.1	+
NO_2	CH_3	NO_2*	None	0.1	0
NO_2	H	CN	HDP	0.01	+
NO_2	H	CN*	None	0.1	0
Cl	H	Cl	None	0.1	0
H	H	H	None	0.1	0
Reference standard— Nitrophenide				0.05	++++

* A description of the preparation of this previously unreported carbanilide is in preparation.

This complex has been examined also for antiparasitic activity in other protozoan infections. These have included *Plasmodium gallinaceum* in chicks, *Trichomonas foetus* in mice, and *Histomonas maleagridis* in turkeys. The DNC · HDP addition compound has about one-tenth of the antimalarial potency of quinine, but there was no evidence of antitrichomonas or antihistomonas activity.

Chemical studies have indicated that in addition to HDP and the 2-hydroxypyrimidine, a variety of other polar compounds yield 1-to-1 molecular complexes with DNC. These include 3-amino-*as*-triazine (AT), 2-hydroxypyridine (PYR), 2-mercapto-4,6-dimethylpyrimidine, formamide, dimethylacetamide, dimethylformamide, tetramethylurea, and acetylpiperidine. Certain hydrochlorides, for example, pyridine hydrochloride and trimethylamine hydrochloride, complexed with DNC in an equimolar ratio, whereas the free bases did not react. The numerous DNC complexes showed varying anticoccidial activity. None was more active than the DNC · HDP adduct.

It was of ancillary interest to examine the behavior of structural analogs of DNC (Table 1) toward HDP under uniform complexing conditions. It is interesting that those carbanilides that gave equimolar complexes with HDP contained at least one electron-withdrawing parasubstituent. Others, for example, 4,4′-dichlorocarbanilide and carbanilide, failed to react. The same effect was observed also in the phenylurea series. Although p-nitrophenylurea and p-cyanophenylurea afforded equimolar complexes, p-chlorophenylurea, and phenylurea did not under the same reaction conditions.

The preparation of the DNC · HDP complex illustrates the general method used in this work (*2*). At room temperature the sparingly soluble DNC extracted exactly one molar equivalent of HDP within 30 min from a stirred methanolic solution. On filtration, a nearly quantitative yield of the equimolar DNC · HDP complex, mp 265° to 275° dec., was obtained. (Analysis calculated for $C_{19}H_{18}N_6O_6$: C, 53.51; H, 4.25; N, 19.71; found C, 53.63; H, 4.30; N, 19.75.) Ultraviolet light absorption in concentrated sulfuric acid: $\lambda_{max}^{m\mu}$ 298, $A_{1\,cm}^{\%}$ 670. The infrared spectrum (Nujol mull) was characterized by disappearance of the N—H stretching frequency (3.03 μ) present in the DNC spectrum, retention of the 5.75 μ C=O band, and shifting or splitting of several maxima in the 6 to 16 μ region. The x-ray powder diagram of the DNC · HDP complex is different from that of either component. Other complexes were similarly identified.

Although it has not been definitely established, hydrogen bonding between the complexing agent and the urea portion of the substituted carbanilide appears likely. In this connection it is noteworthy that Birtwell (*3*) recently postulated a resonance stabilized, eight-membered, hydrogen-bonded, cyclic structure for the urea · HDP equimolar complex. We have assigned the generic name, nicarbazin, to the DNC · HDP complex.

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References and Notes

1. A. C. Cuckler and C. M. Malanga, *J. Parasitol.* 41, 302 (1955).
2. We are greatly obliged to our colleagues, R. W. Walker, J. Wood, and R. N. Boos for analytic data presented in this paper.
3. S. Birtwell, *J. Chem. Soc.*, 1725 (1953).

3 May 1955

Chronic Uncontrolled Cross-Circulation in Unanesthetized Dogs

A technique for performing cross-circulation in anesthetized dogs was described in a previous report from this laboratory (*1*). In that study, the animals were cross-circulated for periods up to 24 hr by means of polyethylene tubing connections between the carotid artery of each animal and external jugular vein of the other. Regulation of blood flow between the partners was not necessary. The present report (*2*) describes a method for cross-circulation in unanesthetized dogs. Eight pairs of dogs were cross-circulated for periods from 47 to 100 hr in the nonanesthetized state.

Under sodium pentobarbital anesthesia, an external jugular vein and carotid artery of two dogs are cannulated with polyethylene tubing (No. 350, Clay-Adams, animal-tested). The necks of the

animals are placed together, and the arterial cannulas of each animal are connected to the other's jugular vein cannula with a short connecting piece of polyethylene tubing (No. 360, Clay-Adams). The necks of the two dogs are then snugly approximated with a plaster cast, leaving the central portions of the cannulas and the connecting pieces exposed. The animals are heparinized prior to and throughout the cross-circulation period, at a dosage of 2 mg/kg every 6 hr.

Recovery from anesthesia is uneventful, and the animals eat and drink well in the postoperative period. Ambulation is difficult in the first postoperative day but is much improved thereafter. A rigid anticoagulant schedule must be maintained if thrombosis is to be avoided. Blood flow may be determined by turning the dogs on their backs and inserting a flowmeter between the artery and vein tubings. Blood flow in our series, as measured with a rotameter, ranged from 200 to 700 ml/min.

Figure 1 shows a pair of dogs that had been in cross-circulation for 72 hr at a flow of 400 cc/min. In Fig. 2 may be seen the plastered necks and connecting tubings. Rectal temperatures do not differ more than 1 deg C in these cross-circulating animals, and blood flows remain relatively constant for days. They may be separated at any time by clamping the connecting tubings and removing the plaster. All eight pairs in this series were electively disconnected and used for studies in homotransplantation immunity. Two pairs were cross-circulated again at a later date, without untoward event.

The procedure of chronic uncontrolled cross-circulation results in rapid and continuous intermingling of the blood streams of the partners. With proper attention to details of cannulation, plastering, and heparinization, the technique is safe for at least 100 hr. There is no reason to believe that longer periods of cross-circulation would be unattainable.

Fig. 1. Pair of dogs in cross-circulation.

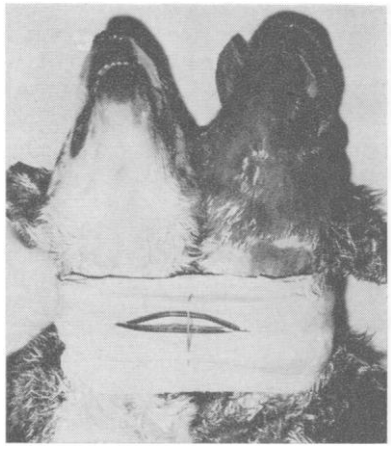

Fig. 2. Necks of cross-circulating dogs. Note nail connecting plaster struts to protect connecting tubings.

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References and Notes

1. R. H. Egdahl, *Federation Proc.* 14, 42, 1955.
2. The opinions and assertions contained in this communication are my private ones and are not to be construed as official or as reflecting the views of the Navy Department or of the naval service at large.

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26 May 1955.

Systematization of Journal Practices

All authors who write for more than one journal must welcome the discussions in these pages [*Science* **121,** 7A (21 Jan. 1955); **121,** 444 (25 Mar. 1955); and so forth] of the advantages of uniform editorial requirements. I should like to add some definite proposals, some of which, I hope, will prove to be generally acceptable.

Although I should like to see a single system for references, I believe that there is too much rugged individualism among editors to hope for this sort of millenium. A more practical goal, it seems to me, would be the adoption of about three standard long forms, such that all the forms of all of the cooperating journals could be obtained by striking out appropriate portions of one of the long forms. This would minimize the difficulties of preparation while requiring only incomplete agreement among editors.

Behind any agreement on style of references, there should be a keen realization that the references are there for the reader, not for the writer and especially not for the editor. To me this necessitates flexibility and the giving of necessary details—flexibility enough, for example, to allow citation of author and date in the text whenever readers are likely to be able to recognize the exact reference from this information. Necessary details will usually include, except possibly in review articles, at least an indication (in the list of references) of the title of each article.

Once upon a time, references to papers were crude and hard to use, at least by present standards. Giving author, journal, and year was thought to be enough. It was not felt necessary either to mention page numbers, or to single out one of the possibly many papers by that author in that volume. Today we do better, except with references to books! Citing a 900-page book without any further detail is apparently quite proper; yet the reader may have more difficulty in finding what is meant than he would have with a "volume only" reference to a journal. If references are to be oriented to the reader's use, then references to books should at least refer to chapters and often to sections.

In passing, it is my observation that more persons read the footnotes than read the text. Whether this is caused by the focusing of attention on rare events, the natural perversity of readers, or the hope of finding a reference to one's own work, I do not know. But if this observation is correct, only the most important statements should go in footnotes. Since this seems unlikely to come to pass, let us eliminate footnotes entirely or, perhaps, put them all together at the end of the article.

As a separate matter of specific technique, let us look at the technique of our legal colleagues, who deal with more references and cross references than most scientists do. They have for a long time found it convenient to place the volume number *before* the periodical's name or abbreviation. Why do we not do the same? Editors may find it strange, but 121 *Science* 444 flows smoothly from my tongue and makes a great saving in punctuation marks and space.

Is it not time for an editor to be heard from now?

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20 May 1955