those urgencies be initiated and extended through appropriate agencies in those areas. As a pattern for such research proposals, it would urge that we seek to establish in each area the relationship between research and practice in that area, which now exists between the physical sciences and engineering and between the biological-medical sciences and medicine. Moreover, it would recognize that the translation of research findings into the daily life, so that our beliefs and practices of living will be informed and guided by research, presents one of the most urgent problems, calling for systematic study of our cultural traditions and of the methods of re-education that will recognize the values in those traditions but provide more effective practices for their attainment.

(12) Finally it would mark the acceptance, by scientists and research workers of all kinds, of the need for developing some scientific statesmanship commensurate with the magnitude of the tasks ahead and with the responsibilities which research now bears and must increasingly carry in the orientation of our national life.

The issues involved in the development of a national policy for research go far beyond the many controversial questions now being debated. They relate to the more fundamental questions of insuring the continuation and the extension of critical thinking as our major resource for advancing human life and social order toward the enduring values of our cultural heritage. If we aspire to the democratic ideal of the value and worth of the human personality, the dignity of man and of woman, we should recognize that the critical thinking of research has been the instrument throughout the ages which has increasingly worked for the attainment of these human values and these democratic aspirations, as formulated in our religion and our arts.

To-day critical thinking and the powers of trained organized intelligence offer possibilities such as no previous age has ever had, for achieving human conservation and advancing our free social order. The instruments are here and their powers and scope are being rapidly enlarged. We must muster the courage and imagination to use those instruments constructively and with full realization of the long-term tasks we face. That is the purpose of a national policy for research, which is not a program or a scheme of planning and control, but a considered declaration of purpose and intentions and of basic aims, to inform individual and group action and institutional programs, to provide the criteria for their decisions and to solicit a commitment to these larger tasks, so that every one will be put on notice that what he does or fails to do will advance or obstruct our national policy for research.

The relation of science to society is more than a question of gadgets or even technology; it involves the provision of knowledge and the criteria by which we can continue the endless task of developing a social order dedicated to human needs and potentialities. This means learning to understand nature and man and his traditional culture and how man can create a way of life directed to his aspirations, as informed by critical thinking.

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SPECIAL ARTICLES

CALCIUM IN PREVENTION AND TREATMENT OF EXPERIMENTAL DDT POISONING

THE mechanism of the toxic effects of dichlor-diphenyl-trichlorethane (DDT) is imperfectly known, whether in invertebrates or vertebrates. Experiments with arthropods, particularly with insects, seem to indicate a poisoning of the nervous system. Many experiments have been made with various vertebrate species, such as pigeons, rats, rabbits, cats, dogs, horses, oxen, goats,[1] frogs and goldfishes.[2] Daily doses of 100 mg of DDT per kg body-weight for a given period are responsible for symptoms which seem to show intoxication of the nervous system. In our experiments with dogs we observed that the symptoms begin with fibrillar contractions of the muscles of the hind legs which afterwards spread through the muscles of the entire body. Continuous contractions of all voluntary muscles, muscle-incoordination and inability to stand are the symptoms then observed. The animal lies down, the muscular contractions persisting for from 12 to 24 hours. As a rule, the animal recovers spontaneously; the intensity and duration of the muscular contractions depend on the dose of DDT administered. It seems to us that these symptoms are similar to those observed in dogs treated with carbon tetrachloride. Minot,[3] who noted the similarity between the symptoms produced by carbon tetrachloride in dogs and those of tetany in children, investigated the effect of intravenous injections of calcium chloride solutions on dogs in state of convulsions and unconsciousness brought about by carbon tetrachloride intoxication. A few (15 to 20) minutes after injecting the calcium chloride solution, the dogs were

[1] A. A. Nelson, *et al.*, *Pub. Health Rep.*, 59: 31, 1944.
[2] M. M. Ellis, B. A. Westfall and M. D. Ellis, SCIENCE, 100: 477, 1944.
[3] A. S. Minot, *Proc. Soc. Exp. Biol. and Med.*, 24: 617–20, 1927.

TABLE 1

THE CURATIVE EFFECT OF CALCIUM GLUCONATE INJECTED INTRAVENOUSLY IN DOGS EXPERIMENTALLY INTOXICATED BY DDT

Dog No.	Weight kg	Quantity of DDT administered up to the beginning of the experiments		Quantity of DDT administered to verify the therapeutic effect of calcium gr	10 per cent. solution of calcium gluconate injected cc	Number of experiments	Time elapsed before recovery Hours
		Daily doses gr	Total doses gr				
1	14	1.4	29.4	2.4	20	1	2
2	14	1.4	9.8	1.4	20	2	2–3
8	12	1.2	7.2	2.2	20	4	1,30–4
9	8	1.2	6.5	2.6	20	1	2
10	18	1.8	27.0	2.8	30	2	2,30–3
11	11	1.1	11.0	2.2	20	2	2–3

As Table 1 shows, calcium gluconate hastens the recovery of the intoxicated dogs. When calcium was not injected, the same dogs intoxicated by daily doses of DDT in the ratio of 100 mg of DDT per kg of body-weight recovered only 12 to 24 hours after the beginning of the symptoms of poisoning. Having induced susceptibility in two dogs (Nos. 5 and 6), doses of 200 mg of DDT per kg of body weight were given to them, and no calcium gluconate was injected. One of the dogs so intoxicated died 20 hours, the other 24 hours, after the appearance of the symptoms.

capable of standing and convulsions were no longer observed. Relapses were frequently noted, but the animals responded well to new injections of the calcium chloride solution. Minot established, too, that the addition of calcium salts to the diet, a week or longer before administering toxic doses of carbon tetrachloride, was effective in preventing the development of symptoms of intoxication.

We intended to verify if intravenous injections of convenient calcium salt solutions could prevent the display of the symptoms of experimentatal DDT poisoning in dogs. Our hypothesis is that DDT provokes a lowering of the calcium level in blood, since only relatively discrete histological lesions in the central nervous system are noticeable, notwithstanding the severe apparently neurological symptoms of intoxication.[1, 4]

Our experiments were made on dogs of undetermined race and varying age and weight. Daily doses of 10 per cent. oily solutions of DDT were administered orally in the ratio of 100 mg of the drug by kg of body-weight until symptoms of intoxication appeared. In some cases slight symptoms of poisoning were apparent after a few days, but then the animals recovered promptly and spontaneously, and only after new administrations of DDT intense symptoms were observable. Afterwards it was sufficient to give 100 mg of DDT per kg of body-weight to have intense symptoms of poisoning with spontaneous recovery 12 to 24 hours later. From then on the susceptibility of the animals to the drug increased greatly. With animals so prepared, we began the experiments to verify the effect of calcium on the development of the symptoms of poisoning, and for this purpose doses of 150 to 200 mg of DDT per kg of body-weight were given. Calcium gluconate (10 per cent. solution) was injected intravenously. In order to investigate the curative power of calcium, calcium gluconate was injected in 6 dogs with severe symptoms of poisoning; to verify its preventive effect, calcium gluconate was administered to 3 dogs, during the three days previous to their taking of DDT and also on the day of the experiment; to another 3 dogs the administration of DDT (orally) was immediately followed by an injection of calcium gluconate (intravenously), and in addition the injection of this calcium salt was repeated a few hours later.

TABLE 2

THE PREVENTIVE EFFECT OF CALCIUM GLUCONATE WHEN INJECTED INTRAVENOUSLY BEFORE AND AFTER THE ORAL ADMINISTRATION OF TOXIC DOSES OF DDT

Dog No.	Weight kg	Quantity of DDT administered up to the beginning of the experiments gr	Quantity of DDT administered to verify the preventive power of calcium gr	10 per cent. solution of calcium gluconate injected cc	Number of experiments	Results
1	14	36,8	2,8	30	2	no symptoms
2	14	30,1	2,4	80 (four daily doses of 20 cc)	2	" "
8	12	16,2	1,2	"	2	" "
9	8	10,4	1,3	30	1	slight symptoms
10	18	39,6	2,8	30	1	no symptoms
11	11	16,4	2,2	80 (four daily doses of 20 cc)	2	" "

Dog No. 11, after having received in due time 3,2 gr of DDT, could not be protected against the toxic effect of the drug by 2 injections of 20 cc of a 10 per cent. solution of calcium gluconate, one of which was administered immediately after giving DDT, the other being injected 4 hours later. Notwithstanding the high quantity of DDT taken, the dog, which presented intense symptoms of poisoning, made good recovery 8 hours after the second injection of calcium gluconate.

[4] R. D. Lillie and M. T. Smith, *Pub. Health Rep.*, 59(30): 979–84, 1944.

Satisfactory results obtained by the use of calcium gluconate in prevention and treatment of dogs experimentally intoxicated by DDT suggest that the apparent neurologic symptoms observed are consequent to hypocalcemia, and not due to direct action of DDT upon the central nervous system. It must be emphasized that the six dogs used in the experiments recorded in the present paper are all but one (No. 9) in apparently good physical condition a month after the ending of the experiments.

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STUDIES ON HUMAN PLACENTAL THROMBOPLASTIN IN VITRO AND IN VIVO

AN extract from human placenta exhibiting thromboplastic activity was first described by Sakurai.[1] Eley *et al.*[2] modified his method and prepared a product which did not prove to be highly active on hemophilic blood.[3] Recently Howell[4] prepared a substance from pig lungs of considerable purity and extraordinary potency. He also succeeded in splitting off the active phospholipid. Since human placenta can be obtained so easily, as compared with human lungs from autopsies, I applied Howell's method for that material. However, the resulting protein compound was not as active and not as soluble in alkaline water as compared with the product from human or pig lung. Therefore, a new method has been developed for both the preparation of a protein phospholipid compound and an apparently protein-free substance as tested by the Biuret reaction. In addition human thromboplastin has been prepared recently from saline plasma obtained by diluting blood 10 to 15 times its volume with physiologic saline. Detailed descriptions of the methods of preparation of both the placental and plasmatic thromboplastic substances will be given in a subsequent article.[5]

The new placental thromboplastic substances compare well in potency with Howell's product from pig lung. *In vitro,* in small doses they have caused rapid clotting of hemophilic blood. The materials contain calcium and phosphorus. They are waxy, whitish and wholly soluble in water. Because of a rather high calcium content, they can coagulate decalcified plasma without the addition of calcium chloride. A single placenta yields a large amount of these substances. Greater thromboplastic activity is obtained from the placenta proper than from the cord. In drying the material, for which several methods have been employed, some loss of potency results.

All *in vivo* studies have been made with the protein compound. Following intravenous injection into dogs, the thromboplastin shortens the coagulation time. In large doses there is an initial prolonging effect upon the coagulation time, in some cases the blood becomes incoagulable. However, after several hours the coagulation times return to their original values previous to injection and even have been found to be shortened. This shortening effect lasted between 3 to 5 days in 3 dogs, and for 2 weeks in 2 dogs. The blood-saline coagulation test of Copley and Houlihan[6] has been applied to these studies. This test allows a better measure of the coagulability of native blood than previous methods which tested only the undiluted native blood. The phenomenon of hypercoagulability for a period up to two weeks, after the introduction of human placental thromboplastin into the circulation, can not be explained at present.

Intravenous injections of human placental thromboplastin alone have been made in 15 dogs without general anesthesia. The blood pressure is either slightly lowered temporarily or not at all. There are no apparent ill effects when the thromboplastin is warmed to body temperature and injected slowly. Two dogs which were anesthetized with veterinary nembutal Abbott (0.45 cc per kgm) and thereafter treated intravenously with thromboplastin died in shock. On autopsy one dog exhibited intravascular and intracardial blood coagulation, whereas the other dog was apparently free of coagulation thrombi. This dog died of heart tamponade as a result of an intracardiac injection of adrenalin which was employed in an attempt to alleviate the acute condition of shock. The combination of placental thromboplastin and nembutal appears to produce experimental shock, a phenomenon which merits further investigation. Before the human thromboplastin can be applied *in vivo* by intravenous injections into humans, extensive studies will have to be conducted.

We used this thromboplastin as a local hemostatic in dog surgery resulting in almost instantaneous coagulation of bleeding surfaces. In experiments on coagulation thrombosis in vessel segments of arteries and veins, coagulation was found to occur in less than

[1] K. Sakurai, *Sei-i-kwai M. J.*, 48: 52, 1929. Cited by Eley *et al.* (see footnote 2).
[2] R. C. Eley, A. A. Green and C. F. McKhann, *Jour. Ped.*, 8: 135, 1936.
[3] W. H. Howell. Personal communication, April 7, 1944.
[4] W. H. Howell. Personal communication, May 18, 1943.
[5] A. L. Copley, to be published.
[6] A. L. Copley and R. B. Houlihan, SCIENCE, 100: 505, 1944.