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Metabolic Effects of Polychlorinated Biphenyls in the American Kestrel

POLYCHLORINATED biphenyls (PCB) have been widely found in wildlife samples[1,2]. PCB are used as plasticizers in plastics, resin and chlorinated rubber[3]. They have been recommended for improving lindane residues[4] and have been shown to increase the insecticidal properties of DDT and dieldrin[5]. PCB are highly stable, insoluble in water and soluble in lipids; so that they can persist and undergo biological magnification in the environment.

Sax[6] reported the toxicity of chlorinated biphenyls as moderate to high. One PCB has been shown to produce chick hydropericardial oedema and growth depression proportional to dietary levels (200 and 400 p.p.m.) of the toxicant[7]. These effects were accompanied by such pathological changes as: cream-coloured pancreas, enlarged haemorrhagic kidney, enlarged adrenal gland, small spleen, dermatitis, defeathering and transient changes in blood glucose, haemoglobin and haematocrit levels. Intramuscular injection of PCB has been shown to increase the rate of steroid metabolism (in bird liver homogenates[8] as has been shown for organochlorine pesticides[9]. Although a cause and effect relationship has not been demonstrated, PCB residues have been associated with decreasing populations of fish-eating birds and birds of prey[1].

American kestrels were trapped, allowed to acclimatize for a week, paired (one male and one female per cage), acclimatized for another week and then placed on *ad libitum* experimental diets. The kestrels' diet consisted of one day old dead cockerels. The dead cockerels were injected in the breast region at either 0·5 p.p.m. or 5·0 p.p.m. (w/w) of either 'Aroclor 1254' or 'Aroclor 1262' (Monsanto trade names for PCB containing 54 per cent chlorine and 62 per cent chlorine respectively) dissolved in sesame oil. The higher dose is roughly equivalent to 2 mg/kg PCB to each kestrel. Cockerels for control kestrels were injected with sesame oil only. It is assumed that the kestrels consumed essentially all of the dietary 'Aroclor', for the only parts of the cockerel not eaten were the beaks and feet, and the pellets regurgitated by the kestrels consisted of cockerel down. Each pair was kept in a burlap-covered 6 × 6 × 8 foot wire cage and fed experimental diet once a day for 5 months. At the end of the test period, the birds were killed, livers removed, and the microsomal fraction was prepared and incubated as described by Conney and Klutch[9]. Radioactive oestradiol and its metabolites were extracted with dichloromethane and separated by paper chromatography[10] with changes in procedure as reported previously[11,8].

Histological examination was carried out on kestrels fed 5 p.p.m. 'Aroclor 1254' for 14 days. A central portion of the liver was removed immediately after death and fixed in Carnoy's fluid for 45 min. Sections were cut at 5 μm. All sections were treated with deoxyribonuclease (0·1 mg/ml. in 0·1 M phosphate buffer (pH 7·5)–0·1 per cent gelatine–0·03 M $MgSO_4$) for 3 h at room temperature to remove DNA which would otherwise stain with azure B. All sections were then stained in azure B (0·1 per cent in 0·1 M citrate buffer, pH 4·0) for 2 h at 40° C, washed briefly with water and differentiated overnight with *t*-butyl alcohol[11]. The density of the staining with azure B was measured cytophotometrically at 545 nm (ref. 12). Ten readings of the per cent transmission of a standard area of cytoplasm were made for each of five control and five experimental livers. The mean for control birds was 39·7 ± 3·3 whereas for the experimental birds it was 26·8 ± 2·6. An analysis of variance of both the individual values and the means gave calculated F values which exceeded the 0·005 tabular F; we therefore conclude that the decrease in percentage transmission is a consequence of the presence of more cytoplasmic RNA in the 'Aroclor'-treated kestrels.

Table 1. *In vitro* MICROSOMAL BREAKDOWN OF OESTRADIOL
Amount of polar metabolites formed in nmoles/g microsomal fraction (sample size, 4 for each group)

Diet	Mean	s.d.
Control	0·00	0·00
0·5 p.p.m. 'Aroclor 1254'	13·66	7·35
5·0 p.p.m. 'Aroclor 1254'	60·50	31·20
0·5 p.p.m. 'Aroclor 1262'	19·06	11·30
5·0 p.p.m. 'Aroclor 1262'	47·96	25·43

A dose-dependent *in vitro* breakdown of oestradiol to a more polar metabolite occurred in livers from kestrels fed either 'Aroclor 1254' or 'Aroclor 1262' (Table 1). There was no apparent difference between the effects of the two 'Aroclors' nor was there any difference between sexes. No such conversion took place in the livers from the control birds.

The increase of hepatic enzyme activity can thus be correlated with an increase of cytoplasmic RNA. Proliferation of the endoplasmic reticulum of rat liver cells following the administration of chlordane[13] and DDT[14] has been noted although these changes were not quantified. Our findings suggest the physiological actions of PCB are similar to those of DDT and its metabolites. This industrial contaminant should be considered as an additional burden to the ecosystem comparable with that imposed by the organochlorine pesticides.

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Connectance of Large Dynamic (Cybernetic) Systems: Critical Values for Stability

Many systems being studied today are dynamic, large and complex: traffic at an airport with 100 planes, slum areas with 10^4 persons or the human brain with 10^{10} neurones. In such systems, stability is of central importance, for instability usually appears as a self-generating catastrophe. Unfortunately, present theoretical knowledge of stability in large systems is meagre: the work described here was intended to add to it.

Most of these large systems, often biological or social, are grossly non-linear, which increases the difficulties associated with them. Here we consider linear systems merely as a first step towards a more general treatment.

We have attempted to answer: What is the chance that a large system will be stable? If a large system is assembled (connected) at random, or has grown haphazardly, should we expect it to be stable or unstable? And how does the expectation change as n, the number of variables, tends to infinity?

Monte Carlo-type evidence[1,2] had suggested that the probability of stability decreased rapidly as n was increased, in some cases perhaps as fast as 2^{-n}, an exponentially-fast vanishing of the chance that the system will be stable. This result, however, was for systems that were fully connected, where every variable had an immediate effect on every other variable. While this case is obviously important in theory, it is not the case in most large systems in real life: not every person in a slum has an immediate effect on every other person, and not every cell in the brain directly affects every other cell. The amount of connectedness ("connectance") is often far below 100 per cent. We have studied how such incomplete connectance affects the probability of a system's stability.

Let the linear system's state be represented by the vector $\mathbf{x}$ ($= \langle x_1, \ldots, x_n \rangle$, where each x_i is a variable, a function of time), and its changes in time by the matrix equation

$$\dot{\mathbf{x}} = A\mathbf{x}$$

To "join the variables at random" is to give the elements in A values taken from some specified distribution. "Non-connexion from x_i to x_j" corresponds to giving the element a_{ji} the value zero. Thus, if the specified distribution has a peak at zero, sampling from it will give the equivalent of a dynamic system with many non-connexions. The connectance, C, of the system can then be conveniently defined as the percentage of non-zero values in the distribution. Thus, if the coefficients are drawn from a distribution with 99 per cent zeros, and if $n = 1{,}000$, then each line of the equation would contain about ten non-zero coefficients, corresponding to a system in which each variable is directly affected by about ten other variables.

Because our work was essentially exploratory, we used the distribution in which the non-zero elements were distributed evenly between $-1{\cdot}0$ and $+1{\cdot}0$. The elements in the main diagonal, corresponding to the intrinsic stabilities of the parts, were all negative, distributed evenly between $-1{\cdot}0$ and $-0{\cdot}1$. Thus each sampled value of A corresponded to a system of individually stable parts, connected so that each part was affected directly by about C per cent of the other parts.

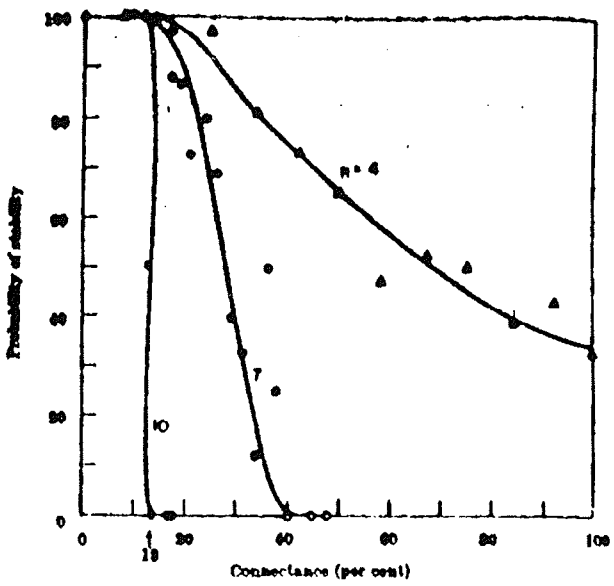

Fig. 1. Variation of stability with connectance.

On a digital computer, a value for n was given and a value for C. Random numbers appropriately distributed were then sampled to provide a matrix A. Hurwitz's criterion was applied to test whether the real parts of A's latent roots were all negative (the stable case) and the result recorded. Further samples, giving further As, allowed the probability of stability (P) to be estimated. The probability was then re-estimated for another value of C, and so on, until the variation of P with C became clear.

The results showed the feature that we wish to report here. As the system was made larger, a new simplicity appeared. Fig. 1 shows a selection of the results, enough to illustrate the principal fact.

When $n = 4$, the probability that the system would be stable depended on C in a somewhat complex curve (which could perhaps be predicted exactly). But as n increases, the curve changes shape rapidly towards a step-function, so that even when n is only 10, the shape might be so regarded, at least for some practical purposes. Thus, even at $n = 10$, questions of stability can be answered simply by asking whether the connectance is above or below 13 per cent: 2 per cent deviation either way being sufficient to convert the answer from "almost certainly stable" to "almost certainly unstable".

The matter is being investigated further, but it may be of general interest to notice that this work suggests that all large complex dynamic systems may be expected to show the property of being stable up to a critical level of connectance, and then, as the connectance increases, to go suddenly unstable.

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