A combination of properly-conducted short-term tests for mutagenicity and long-term animal carcinogenicity studies provides a satisfactory basis for assessing carcinogenic risk for man

Text of Dr. F.J.C. Roe's contribution (as proposer) to Debate D4 at IUPHAR 9th International Congress on Pharmacology (NB Dr. Bruce Ames was the chief opposer)

Something akin to a mere toss of a coin determined whether I proposed the motion for this debate or opposed it.

Against - what at one time seemed to be - an overwhelming tide - I have for more than 10 years been saying - as loudly and as often as I could - two very important things. Firstly that the way in which long-term carcinogenicity tests in animals are presently carried out generates both falsely-positive and falsely-negative results. And secondly that hormonal disturbance rather than exposure to genotoxic carcinogens is responsible for the majority of neoplasms that arise in present day safety evaluation toxicity tests on substances such as drugs, food components and food additives. This is certainly true for rats and probably true also for mice.

Until recently, I thought that my opponent in today's debate - for whom I share with everyone here the most profound admiration and respect - I thought that he believed that genetic damage is the first and most important determining event in the origin of all neoplasms and that, as far as possible, exposure to any chemical found capable of causing mutations should be avoided. If that was at one time his view then it seems that he has recently modified it - perhaps in the light of the huge number of chemicals and other agents which have now been shown to be capable of causing genetic damage.

I suspect that he has come to accept, as I do, that the real problem that today's debate addresses, is not how can one best detect agents which have the capacity to damage DNA or to promote tumour formation by a non-genotoxic mechanism - that is not the question. The question is how can we best identify factors that, under various realistic environmental conditions, actually contribute to the human cancer burden.

One of the tragedies of our time is that pharmacologists opted out of - or at least lost control of - the field of carcinogenesis particularly as it relates to hormones and drugs. Instead - and for far too long - the evaluation of carcinogenic risk has been in the hands either of so-called toxicologists who have no basic training in pharmacology - or, worse still, in the hands of mere number crunchers, lawyers or politicians - who are devoid of all biological training. Consequently a series of disastrously wrong assumptions have formed the basis of both testing and decision-making.

Let me illustrate some of these false assumptions:-

Slide 1

Slides 1 - 6

I could list other false assumptions - but the point I am making is that my concept of a properly conducted carcinogenicity test in animals is one in which these assumptions are not made. When Ramazzini, the father of occupational medicine, observed in 1700AD that cancer of the breast is more common in nuns than in other women, I doubt whether he would have predicted that in the 1970's and 1980's there would be thousands of researchers advocating a hunt for Ames +ve chemicals in Convents. On the other hand, what would he have thought about the sense of looking for carcinogens by carrying out tests in rats under conditions in which a majority develop both pituitary tumours and multiple tumours of mammary gland origin?

Thus, my concept of a properly conducted carcinogenicity test in animals has two features. Firstly it should be conducted under conditions in which untreated control animals remain free from laboratory-induced disease, particularly neoplasia secondary to overfeeding. Secondly if tests are carried over a dosage range that extends, in real terms - that is to say after taking absorption metabolism and pharmacokinetic data into account - to high multiples of the doses to which humans are exposed - then

interpretation should be embarked on in the full knowledge that the circumstances are not realistic and that interference by non-specific effects is likely.

My experience during recent years is that the only drugs that survive carcinogenicity testing without one or more tumour problems are those with a low therapeutic margin. Virtually all drugs of low general toxicity run into problems and virtually all the problems are in some way hormonal in nature. Such drugs tend to give completely negative results in the Ames test and other validated in vitro and in vito tests for mutagenicity and clastogenicity.

In proposing the motion before the House, therefore, I lay great stress on the words "properly conducted", particularly in relation to the long-term tests.

Moreover, I am not at this stage, put off by the fact that, at present, Regulatory Authorities generally are continuing to require tests to be conducted in an improper way. Also, no drug company has, as far as I know, had the courage to undertake a carcinogenicity test under conditions which avoid overfeeding.

I am optimistic that we are approaching a new era when the improprieties of present-day testing will be put right and, when they are, I shall feel very comfortable with the Motion, provided that common sense and the full force of pharmacological and toxicological science are exercised in the interpretation of studies.

One may look at species so outwardly different as man, mouse and elephant and wax poetic either about the differences or about the similarities. For me there is a comity of qualitative biological responsiveness between such species which far transcends the differences in their outward appearances. The fact that species differ markedly in quantitative response is something that the professional toxicologist can cope with.

I leave one final thought with those who have any doubts about whether to support the Motion. If you vote against it, how would you propose to deal with the vacuum? The epidemiologist won't be in a position to help you. The specialist in strucure-activity relationshiops has come a long way towards being able to predict theoretical genotoxic or clastogenic risk but he's a long way off being able to quantify such risk. Finally, for the seemingly unlimited variety of mechanisms involved in non-genotoxic carcinogenesis, neither the structure-activity specialist nor the molecular biologist is anywhere near being able to predict possible risk for man.

I am sure that my opponent will now seek to dazzle you with his erudition and his new ideas on the possibilities for predicting and preventing genotoxic carcinogenicity, but these ideas are still on the frontiers of knowledge and do not adequately cover non-genotoxic carcinogenicity. Therefore I do not believe that he can, at the present time, offer us anything better than "A combination of properly-conducted short-term tests for mutagenicity and long-term animal carcinogenicity studies as a satisfactory basis for predicting carcinogenic risk for man"

FALSE ASSUMPTIONS

MECHANISMS DON'T MATTER - A CARCINOGEN IS A CARCINOGEN - ALL CARCINOGENS SHOULD BE BANNED.

AN AGENT WHICH PRODUCES A BENIGN TUMOUR AT ANY SITE IS JUST AS MUCH A CARCINOGEN AS ONE THAT PRODUCES A MALIGNANT TUMOUR AT ANY SITE (E.G. A PITUITARY ADENOMA IN A RAT ≡ A LUNG CANCER IN A MAN).

IT IS LOGICAL, SENSIBLE AND FEASIBLE TO BAN ANY CHEMICAL THAT HAS INCREASED THE RISK OF ANY KIND OF TUMOUR UNDER ANY CIRCUMSTANCES.

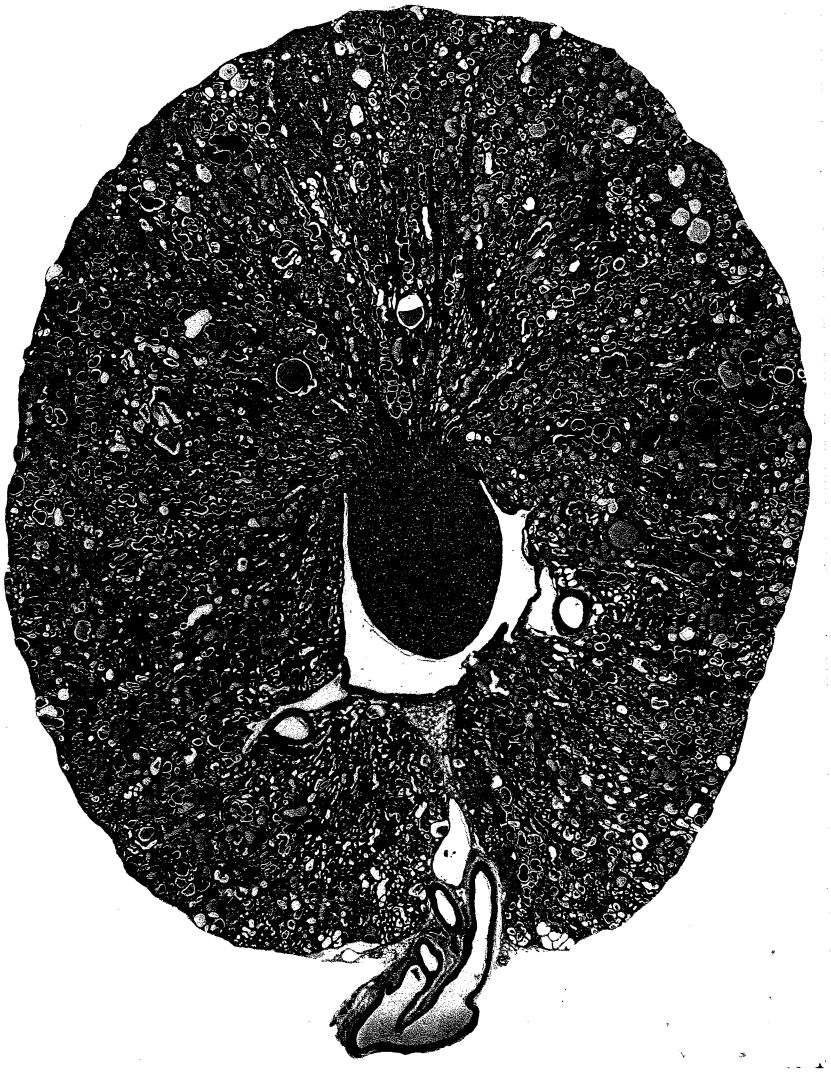
IN ANIMAL TESTS IT DOESN'T MATTER WHAT OR HOW MUCH ANIMALS EAT AND IT DOESN'T MATTER THAT THEY HAVE NO EXERCISE ETC. PROVIDED THAT THE CONDITIONS ARE THE SAME FOR TREATED AND CONTROL ANIMALS.

Hormone-associated neoplasms (%) in ad libitum fed untreated control Sprague Dawley rats observed for up to 26 months (86 rats of each sex)

		♂	♀
Pituitary		31	63
Adrenal	- cortex	2	7
	medulla	51	8
Thyroid	- C-cell	8	8
Parathyroid		0	1
Pancreas	- exocrine	33	0
	endocrine	16	9
Testis		7	-
Ovary		-	5
Mammary gland	- fibroadenoma		76
	adenoma	5	12
	other		29

(from Kociba et al, 1979)

Slide 3



Kidney from a male Wistar rat fed ad libitum for 24 hours/day for 2 years.

Kidney from a male Wistar rat fed ad libitum for 6½ hours/day for 2 years.

Effect of dietary restriction on incidence of pituitary and mammary tumours in rats†

	Males		Females	
Feeding regimen . . .	*Ad lib.*	Restricted	*Ad lib.*	Restricted
Rats with pituitary tumours (%)	32	0•••	66	39••
Rats with mammary tumours (%)	0	0	34	6•••

••$P<0.01$, •••$P<0.001$.

Effect of simple dietary restriction on tumour incidence in mice†

no. of mice which developed tumours at any time during the study. There were 160 mice of each sex in each group

	Males		Females	
Feeding regimen ...	*Ad lib.*	Restricted to 75% of *ad lib.*	*Ad lib.*	Restricted to 75% of *ad lib.*
Type of tumour				
Lung	30	19*	24	8**
Liver	47	12***	7	1*
Lymphoma	4	1	11	4*
Other	8	4	12	4*
Any tumour at any site	71	36***	50	17**
Any malignant tumour	17	7*	23	7**

*$P<0.05$, **$P<0.01$, ***$P<0.001$.
†Conybeare, 1980.

Dietary fat and liver tumours in C57BL female mice•

	Mice with liver tumours (%)	
	Benign or malignant	Malignant
SS diet with 5% GNO	8	1
SS diet with 10% GNO	43	9

GNO, groundnut oil.
•Gellatly, 1975.

% CAUSES OF DEATH IN HUMANS (AGED 15-74) AND IN LABORATORY RATS

	HUMANS*		RATS	
	MALE	FEMALE	MALE	FEMALE
NEPHRITIS/NEPHROSIS				
- FATAL	0.7	-	-	-
- DEBILITATING/FATAL	-	-	60†	65†
ENDOCRINE, NUTRITIONAL AND METABOLIC (EXCEPT DIABETES & DEFICIENCY)				
- FATAL	0.2	0.5	-	-
- DEBILITATING/FATAL	-	-	↑80†	↑100†
NEOPLASIA OF ALL ENDOCRINE SITES INCLUDING PITUITARY	0.1	-	↑20†	↑80†
- PITUITARY ONLY	-	-	20.5‡	40.5‡
NEOPLASIA OF BREAST	-	7.1	2.7‡	40.5‡
ISCHAEMIC HEART DISEASE	31.9	20.6	0	0

* MORTALITY DATA FOR ENGLAND AND WALES FOR 1970-72

\+ TYPICAL DATA FOR AD-LIBITUM-FED RATS

‡ DATA FROM 220 MALE AND 220 FEMALE AD LIBITUM-FED, UNTREATED SPRAGUE-DAWLEY RATS WHICH CONSTITUTED THE CONTROL GROUPS IN TWO RECENT CARCINOGENICITY STUDIES.

OVERFEEDING AND NEOPLASIA OF THE PARATHYROID AND ADRENAL MEDULLA IN RATS

OVERFEEDING ⟶ CHRONIC PROGRESSIVE NEPHROPATHY (CPN)

CPN ⟶ PARATHYROID HYPERPLASIA AND NEOPLASIA

EXCESS PARATHORMONE ⟶ 1. HYPERCALCAEMIA
2. METASTATIC CALCIFICATION (AORTA/KIDNEY)

HYPERCALCAEMIA ⟶ ADRENAL MEDULLARY HYPERPLASIA AND NEOPLASIA