Francis Bacon (Seite 290) „die Beziehung des modernen Menschen zum Tier in besonders radikaler Weise" durchspielt (Seite 296): „Was Leben ist, manifestiert sich für Bacon demnach gerade auch am Tier. Für ihn ist ethisches Verhalten zu Mensch und Tier bedingt durch das Wissen um die gemeinsame Animalität, des Geworfenseins, der Sterblichkeit. Er fühlt sich ebenso ausgesetzt wie das Tier, ebenso verletzlich." Am Beispiel der Werke auch anderer Künstler geht Baum der Frage nach, welche Rückschlüsse von der Art der Darstellung der Tiere auf die Haltung der mit den Tieren abgebildeten Personen und somit auf die Haltung der Gesellschaft Tieren gegenüber gezogen werden können (Seite 311): „Wenn Beuys Tiere als ‚Engelswesen', als ‚Götter' bezeichnet, so transzendieren beide Künstler die Beziehung des Menschen zum Tier... Die Botschaft der Kunst lautet, das Tier als Teil der eigenen Kunst anzuerkennen."

In seinem detaillierten musikhistorischen Beitrag **„Das Tier als Musiker"** führt **Marcel Dobberstein** aus, wie sehr seit der Antike Tiere mit der Musik verknüpft sind. Bereits damals wurden Teile des Tierkörpers zum Bau von Instrumenten verwendet oder Instrumente mit Tiersymbolen verziert. Ritualtötungen von Tieren wurden mit Musik begleitet, und auch aus Sagen wird die enge Verknüpfung zwischen Tieren und Musik deutlich. So wurden Tier-Gott-Mischwesen häufig als Musiker dargestellt. Anhand verschiedener Beispiele von Tierlauten als Elementen in der Musik – von Beethovens „Pastorale", über Mozarts „Spatzenmesse" bis hin zum „Karneval der Tiere" und dem Musikstück „Peter und der Wolf", führt Dobberstein aus (Seite 328): „Mit Anbruch der Neuzeit hält das Tier selbst in die Musik Einzug."

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Meinungen und Kommentare

Kay Brune

Replacement and Refinement of Animal Experimentation in Drug Research has been and will be a Permanent and Necessary Process

Many lay people and some physicians believe that animal experimentation has not led to the discovery and better use of important drugs. This is not true as will be exemplified in this article: Even the oldest remedies were only made useful to mankind by animal experimentation.

However, as these examples also show, it is a continuous process in drug research to supplant self- and animal experimentation by *in vitro* technologies, and also to make animal experiments more acceptable by refinement. Experience has taught us the following two lessons:

1) If a new active substance (principle) is discovered, analogues may be developed primarily by using alternative methods.

2) This holds true for the detection of known types of toxicity, but not of so far unknown toxic reactions. (A recent example is the development of iris overpigmentation by the anti-glaucoma drug latanoprost which was discovered in the clinic and could so far not be mimicked in tissue culture systems.)

On the other hand, completely new drugs (therapeutic principles) are hard to find without animal experimentation. Sir John Vane, the famous Nobel Laureate, said when he was asked why he still used tissues from animals to find new drugs and new substrates of drug activity: "I'm not aware of a drug which has been found by a gas chromatograph." Therefore, let us examine how the first pure drugs were discovered, how animals contributed and how one may find new compounds for the same indications using 3R approaches:

1) **Opium** is certainly one of the oldest remedies in human use (Macht, 1915; Tainter, 1948; Kritikos and Papadaki, 1967). The resin of the growing poppy fruit was already collected and used by the Babylonians and Egyptians. Whether they observed the effect of poppy first in animals or themselves, or whether they got this miracle drug as a gift from the gods – as is often claimed – is unknown. Many antique relics depict such divine help (Kritikos and Papadaki, 1967). Apart from morphine, poppy resin contains papavarin, codeine, noskapine and several other active ingredients in variable concentrations. Since the old physicians did not know the morphine content of a certain "remedy", correct dosing was very difficult. It is reported by Galenus that shopkeepers and quacks distributed opium against diarrhoea, cough and pain, but in an uncontrolled manner, occasionally causing death (Tainter, 1948; Kritikos and Papadaki, 1967). Galenus' complaints indicate that patients often died from an overdose of morphine. The same problem is still common in drug addicts who inject morphine or heroine of unknown quality and concentration and die when the drug is particularly "good".

A solution to this problem came only when F. W. Sertürner (Fig. 1) in Einbeck,

Fig. 1: F. W. Sertüner (1783-1841)

Germany, in 1806 took advantage of his large pharmacy (drug store) being protected by several dogs. He started extracting the active ingredients from poppy resin. He was searching for the sedative component of opium resin and tested his extracts on his dogs (one died). By this early combination of pharmaceutical extraction methods and animal experimentation he isolated a basic crystalline compound, which he termed "morphium" (Sertürner, 1806). Physicians soon took advantage of this new pure drug which could be administered at an exact dosage and could be given parenterally. It may be added here that Sertürner did not define the lethal dose of morphine in animals but jumped directly to self-experimentation. After giving about three times higher doses than allowed today to himself and several friends, he narrowly escaped death due to respiratory blockade (Sertürner, 1806; Macht, 1915;).

The method developed by Sertürner became the basis of the extraction of so-called alkaloids, i.e. natural ingredients of plants, which comprise organic bases and crystallise under certain circumstances. The first scientists who copied Sertürner's approach were the French chemists Pelletier and Caventou (Fig. 2). They isolated quinine, quinidine and many other alkaloids by this method (Macht, 1915). Others followed and produced veratrine, strychnine, etc. The isolation of many others, such as atropine, ephedrine, pilocarpine, muscarine, nico-

Tab. 1: Natural products in medicinal use in man. These "old" compounds have been isolated with animal experimentation. This research was necessary for developing isolation methods (Sertürner), defining the right dose (digitoxin) and developing more suitable (synthetic) analogues. The latter process always took advantage of newly developed *in vitro* methods.

Drug Targets	Natural Products	Today's Use	Historical Use of Animal to Prepare for Human Use	Possibilities Today *(in vitro)*
activating agents	caffeine	mood enhancer	mode of action	cell culture
(CNS)	cocaine	activator	isolation, dosage	cell cultures, slices
analgesics	codeine	mild pain	isolation, dosage	slices
	morphine	serious pain	isolation, dosage	slices, receptors
	salicylate	traumatic/ rheumatic pain	?, aspirin tested in animals, s. text	for ulcerogenic act.: animals
blood coagulation	hirudin	thrombosis	isolation, dosage	*in vitro* coagulation
(thrombosis)	hydroxycoumarin	embolism	discovered in cows, tested in rodents, used also as rat poison	liver cells
cardiovascular	quinidine	arrythmias	isolated as morphine, tested in dogs and rodents	heart cells
system (insuff.	digitoxin (digoxin)	cardiac insuff.	tests for of biological activity in rodents	heart cells
arrythmias)	reserpine	hypertension	isolation, dosage	?, (no convincing alternative)
bronchi/lung	codeine	antitussive	isolated as morphine, tested in dogs and rodents	?, (no convincing alternative)
(asthma, cough)	ephedrine	bronchodilatator,	isolation, mode of action	smooth muscle strips
	guaifenesin	expectorans	?, mode of action, dosage	?, (no convincing alternative)
gastrointestinal system	atropine	(ulcers)	isolation, definition of biol. activity	heart cells, smooth muscle strips
(obstipation,	antrachinone	laxative	?, historical use for purgation	
diarrhea)	ricinoleic acid	laxative	?	?, (little interest)
local anaesthetics	cocaine	local analgesic (skin, mucosa)	isolation, dosage	nerve – skin preparation
muscle/joint	colchicine	gout	isolation, definition of biol. activity	isolated leucocytes
(pain, inflammation, preparations	tubocurarine	anaesthesia	isolation, mode of action, dosage	nerve-muscle
spasms)				
ocular system	physostigmine	glaucoma	frog heart: mode of action, isolation, dosage	isolated heart, receptors
sedatives	atropine	(agitation)	s. above	slices
(CNS)	(morphine)	(agitation)	s. above	slices
	reserpine	(sleep extension, dream intensification)	definition of the mode of action, dosage	? (no convincing alternative)

Fig. 2: Caventou and Pelletier (and quinine)

tine – to name just a few – was also facilitated by Sertürner's work. In other words the early pharmacopoeia was based on alkaloids isolated by methods first applied to opium and tested in dogs. Many of these drugs are still in use today. It would be false to say that they were developed without animal experimentation. It may, however, be assumed that only few animals were sacrificed to allow for the medicinal use of these compounds (Tab. 1).

2) Another drug that is often claimed to be a pure natural product discovered by ancient mankind and in clinical use for millennia is **salicylic acid**. Indeed the old Greek and Roman physicians used extracts of willow bark and other salicylic acid ester containing plants against painful inflammation and skin irritation. Only in the 19th century Piria in Italy and Löwenich in Switzerland isolated the pro-drug of the active ingredient, namely salicylic acid glycosides. Finally, Kolbe from Marburg, Germany, came up with pure salicylic acid. The full activity of this drug in rheumatoid arthritis was discovered by Stricker (1876). (For review see Brune, 1997.) Nevertheless the real blockbuster was aspirin (acetylsalicylic acid) synthesised by a young chemist at the company Bayer in Leverkusen, Germany. He believed that this derivative of salicylic acid was not only more palatable, but also less harmful to the human mucosa. To prove this, the first pharmacologist at Bayer, Heinrich Dreser, developed an "ingenious" system (Dreser, 1899): He used living goldfish, believing that the "mucosa" of their fins was an analogue of human intestinal mucosa. Dipping the tail fins of (living) goldfish into solutions of either salicylic acid or aspirin, he observed that higher concentrations of aspirin than of salicylic acid were necessary to "cloud" the clear fins (Fig. 3). He concluded that this was proof of a lower toxicity and thus better GI tolerability of aspirin. A dogma that still prevails, despite the fact that Heinrich Dreser himself recognised his error: He didn't measure a "gastrotoxic effect", but rather "acidity", and salicylic acid is more acidic than aspirin (Dreser, 1907).

3) Finally another major discovery of an active ingredient (**digitoxin**) was primarily performed in man. It based on the use of foxglove against dropsy in folklore. William Withering (Fig. 4) fell in love with one of his patients, who was a painter (Withering, 1775). He tried to impress her with bouquets of flowers and detailed knowledge of plant use in medicine. This led him to take the folkloric use of foxglove against dropsy more seriously. He made concoctions of foxglove plants and used them in patients – in part without success, because the patients did not suffer from cardiac insufficiency but rather from tuberculosis, in others with success. However most patients complained of side effects. This was due to the variable concentration of the active ingredient digitoxin in the concoctions, which in case of overdose caused headache, visual disturbance, arrhythmia and occasionally death. Only about 100 years later experimental pharmacology developed a method to define the content of the active ingredient: live guinea pigs, later isolated guinea pig hearts, were exposed and the lethal dose defined in each extract. This biological standardisation led to worldwide medicinal use. Today chemical analysis is doing the job.

Fig. 4: William Withering (1741-1799)

These examples from the early days of drug discovery and development may demonstrate that medical progress in drug development was impossible without animals. Sertürner did harm his dogs and put himself and his friends at risk, because he did no safety testing. One dog died but all the others survived as did Sertürner and his friends after a more or less prolonged period of sleep. The goldfish in the hands of Dreser were killed or died during the experiment. These latter experiments may be regarded as examples of superfluous and totally marketing-oriented research. Still, the aim to search for less gastrotoxic substances than aspirin has led to new compounds which are now substituting for the use of aspirin. The assessment of the biological activity of digitoxin and many other plant extracts was done with biological substrates (for more than 100 years). Without this biological standardisation, which is now supplanted by animal-free methods, medicinal use in man would have been impossible. Even searching for new drugs may and should be performed in tissue culture since receptor constructs and synthetic organs may be produced in tissue culture from stem cells. Long-term toxicity can, however, as yet not be defined *in vitro*. Also, tissue cultures show no blood circulation

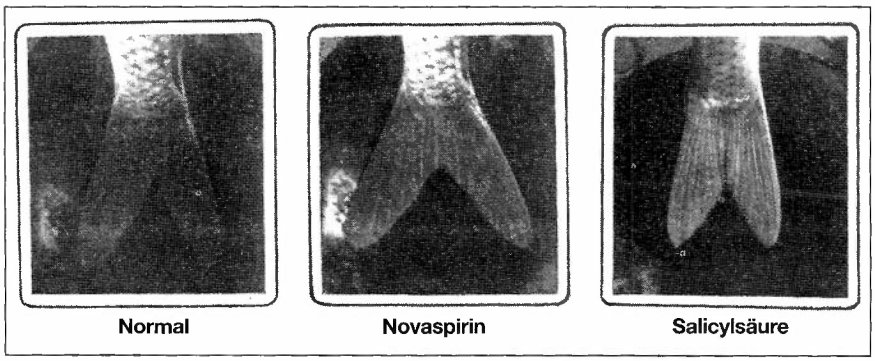

Fig. 3

and artificial hearts degenerate quickly as do *in vitro* neuronal networks and other analogues of "real" tissue. This, however, may change in the next decades – many research groups are engaged in such attempts!

In **conclusion** the examples given demonstrate that our medical knowledge of today is fundamentally based on animal experimentation. Some of the most commonly used drugs worldwide were discovered and made useful to man only following animal experimentation. They also show that drug research has always attempted to simplify research and to reduce animal use. This inherent process has lately been accelerated by financial constraints, the availability of improved technologies (high throughput screening) and an increased awareness of scientists and the public that animal care is not a negligible issue. This is an ongoing process which will lead to more and more replacement and refinement, but not to a complete substitution of animal use. The complete elimination would at present stop our scientific progress and endanger our human population.

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Correspondence to

Prof. Dr. med. Dr. h.c. Kay Brune
Doerenkamp-Professor for Innovations in Animal and Consumer Protection
Department of Experimental and Clinical Pharmacology and Toxicology
Fahrstr. 17
D-91054 Erlangen

Unterschiedliche Reaktionen auf Michael Mierschs Artikel in der *ZEIT* „Intelligenztest für Bestien"

In der *ZEIT* vom 13.11.2003 erschien ein sehr nachdenklich stimmender Artikel von Michael Miersch. Untertitel: „Bei Blutegeln, Tintenfischen oder Rabenvögeln entdecken Wissenschaftler verblüffende geistige Fähigkeiten. Im Tierreich wimmelt es von Genies. Jetzt bröckelt die Sonderstellung der Affen." Der Artikel kann im Volltext gefunden werden unter www.zeit.de/ 2003/47/N-Tiersinne.

Der Autor versucht, die Sonderstellung des Menschen gegenüber den Tieren über die Beherrschung der Sprache zu definieren. Er zählt viele z.T. sehr verblüffende geistige Leistungen von Tieren auf, von denen Nichtbiologen diese kaum erwartet hätten. Zitat: „Das menschliche Bewusstsein ist vermutlich einzigartig, vieles deutet darauf hin, dass kein anderes Lebewesen diese Form des inneren Erlebens mit uns teilt. Vermutlich hatte der Bischof von Polignac Recht, als er im 18. Jahrhundert zu einem Schimpansen sagte: Sprich, und ich werde dich taufen." Der Artikel ist dazu angetan, z.B. *„frutti di mare"* künftig etwas weniger sorglos zu konsumieren oder vielleicht deren Konsum ganz zu unterlassen. Zumindest aber zu akzeptieren, dass Tintenfische tatsächlich in der Tierschutzgesetzgebung vieler Länder eine Sonderstellung einnehmen, sie sozusagen zu Säugern ehrenhalber ernannt wurden. Was dazu führt, dass Versuche mit ihnen genehmigungspflichtig sind.

Wir haben in *ALTEX* jedoch schon mehrfach darauf hingewiesen, dass es gefährlich sein könnte, wie es gerade in den USA gang und gäbe ist, unser (Wohl) Verhalten Tieren gegenüber von deren geistigen Leistungen abhängig zu machen. Entsprechend zurückhaltend hat sich *ALTEX* auch immer verhalten, wenn es um „Menschenrechte für Menschenaffen" ging. Wir denken in der Redaktion, dass es genügen muss, Tieren ihre Tierrechte zu belassen, die sie unabhängig von unserer Einschätzung ihrer geistigen Leistungen besitzen. Mäuse haben Mäuserechte und Affen haben Affenrechte, so wie wir Menschen Menschenrechte haben (sollten).

Während in Tierschutzkreisen der Artikel Mierschs z.T. recht wohlwollend aufgenommen wurde (ein *google-research* dazu ist sehr aufschlussreich) ärgert sich Helmut F. Kaplan ungemein darüber. Er schreibt: „Die Position, die Michael Miersch in seinem Beitrag ‚Intelligenztest für Bestien' in der *ZEIT* vom 13. November 2003 darlegt, ist zugegebenermaßen schwer zu knacken. Das liegt allerdings nicht daran, dass seine Argumentation so schlüssig wäre, sondern daran, dass er keine hat. Miersch bedient sich einer ‚Logik', der ich nicht zu folgen vermag. Seine Methode erinnert an das auf Rummelplätzen und Bahnhöfen beliebte Hütchenspiel, bei dem die Betreiber versuchen, die Spieler durch schnelle Handbewegungen zu verwirren." Im vollen Wortlaut nachzulesen unter http://tierrechte-kaplan.org/kompendium/a241.htm.

ALTEX würde sich über eine rege Diskussion zu diesem Thema sehr freuen.

Die *ALTEX*-Redaktion Zürich