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MICE TIMES

Experiments in animal embryos or fetuses – is it really necessary? Two examples.

The path to an artificial womb

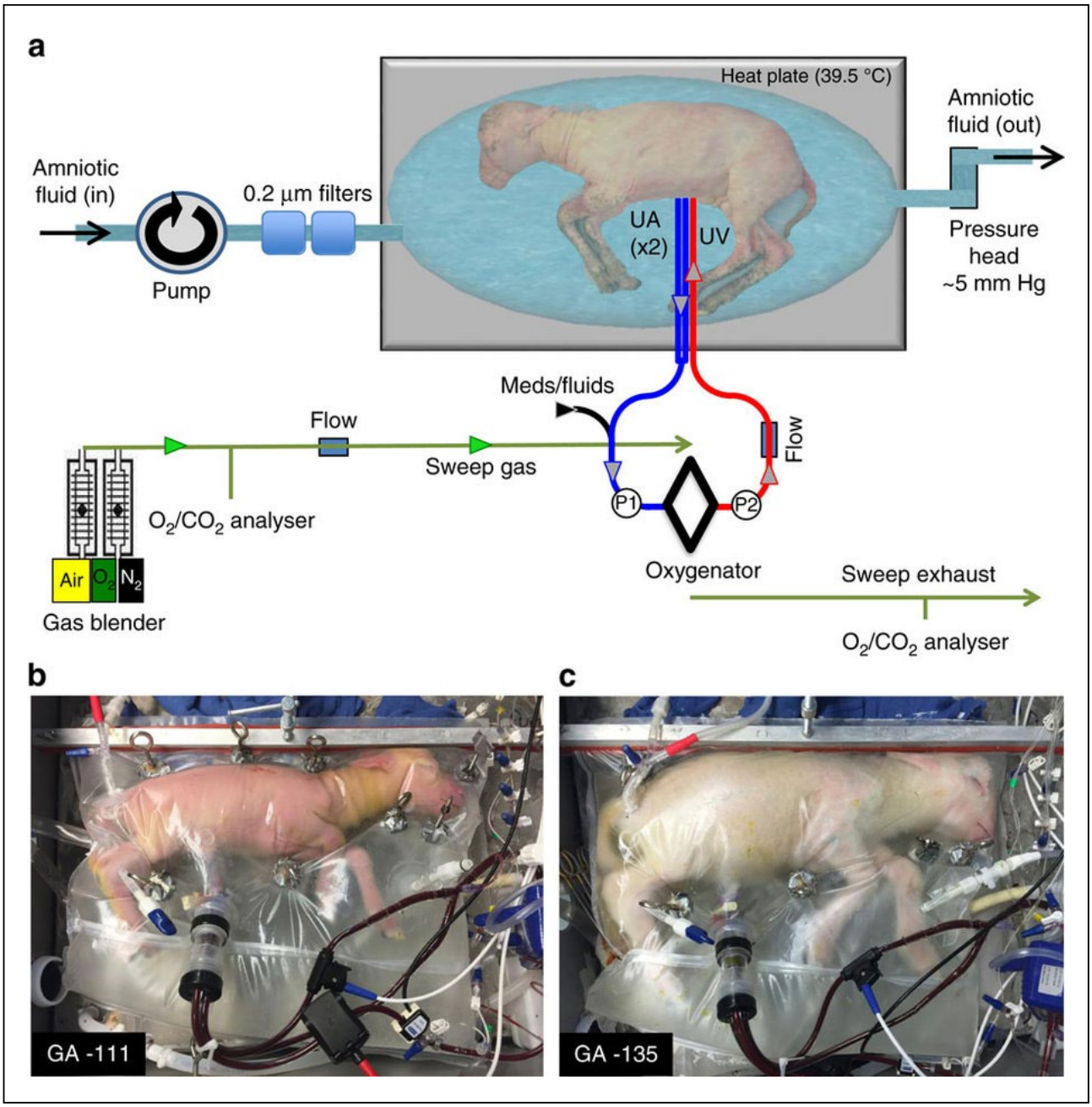
A US study by the Children's Hospital of Philadelphia made in international headlines in recent weeks: "The artificial womb is here", "'Plastic womb' could help premature babies" or "Plastic bag could some day save extreme preemies". A research team led by pediatric surgeon Alan Flake had kept fetal lambs alive outside the mother's womb for up to four weeks[1]. The animals, which were not actually viable, spent several weeks in a fluid-filled "biobag". This bag simulated the conditions in the uterus that supplies lambs with oxygen and nutrients through the umbilical cord.

The animals were delivered by caesarean section 40 to 25 days before the end of the actual gestation period of 145 days and, in terms of development, were thus comparable with extreme preemies, i.e. babies born before 28 weeks' gestation. Thanks to technical advances, babies born before the 23rd week of pregnancy are already capable of surviving today, but sometimes at high cost. The lungs are still immature, and there is a risk of the brain not being supplied with enough oxygen and of lasting damage, e.g. to hearing, eyes or other organs.

Babies born much too early are not yet able to breathe unaided. They are assisted by a machine that blows warm air into their lungs. This kind of artificial respiration is not good for the delicate lungs and fetal heart. The compressed air can cause lasting damage to the tissue. "But without artificial respiration, the baby would die, so we accept the risk of lung damage in order to keep the child alive," says George Mychalska, specialist in fetal surgery at C. S. Mott Children's Hospital at the University of Michigan[2]. The new system developed by Alan Flake and his colleagues manages without a pump. The oxygenated fluid in the cannulas, which are connected to the umbilical cord, pumps the fetal heart of the lambs itself.

For more than 50 years, attempts have been made to develop an artificial amniotic sac that offers prematurely born babies optimum survival chances. The efforts with new technology in lambs now appear to have brought genuine progress. "The experiment could be a milestone for the care of preemies in humans," writes Kathrin Zinkant in the Süddeutsche Zeitung[3]. The development of the lambs was at least stable in the biobag, the lungs matured normally, and brain development ran a normal course, as did general growth. "In principle, the findings obtained can be extrapolated to humans," says Thomas Kohl from the German Centre for Fetal Surgery in Giessen. But the situation of extremely premature babies, he added, will improve little initially, because the technology has to be developed further, and this will take years.

A crucial step has been taken in the direction of the artificial amniotic sac. At present, it impossible to assess reliably whether the method presented can really increase the viability of extremely premature babies without additional morbidity, even though the results make survival for longer than one or two weeks a realistic prospect for the first time, says Katrin Klebermass-Schrehof from Paediatric Intensive Care Medicine and Neuropaediatrics at the Medical University of Vienna. "Animal experiments can only ever be extrapolated to the human organism to a limited extent, but they nevertheless provide important clues for possible use in humans," she explains. Fetal surgeon Mychalska from Michigan expects an artificial placenta to be available for humans by 2021 thanks to the advances being made.



(a) Circuit and system components consisting of a pumpless, low-resistance oxygenator circuit, a closed fluid environment with continuous fluid exchange and an umbilical vascular interface. (b) Representative lamb cannulated at 107 days of gestation and on day 4 of support. (c) The same lamb on day 28 of support illustrating somatic growth and maturation.
Source: Emily Partridge et al., An extra-uterine system to physiologically support the extreme premature lamb; Nature, 25. April 2017

The path to safe medicines

Until well into the 1950s it was assumed that the placenta was an impenetrable barrier that reliably and completely protects the embryo from outside influences. In 1961 came the rude awakening. Women who had taken the apparently harmless medication Contergan for morning sickness during pregnancy gave birth to babies with missing limbs. The medicine with the active ingredient thalidomide had been marketed by Grünenthal since 1957. Four years later, it was withdrawn from the market. Altogether, more than 10,000 babies were born with congenital defects.

"Grünenthal had only tested thalidomide in rats before launching it onto the market, and even in pregnant animals no abnormalities were observed in these tests," says toxicologist Friedlieb Pfannkuch, who for many years was entrusted with the investigation of adverse effects of substances in the pharmaceutical industry. "Later on, tests were carried out in pregnant rabbits, and here malformations then occurred in the embryos during treatment with thalidomide," says Pfannkuch.

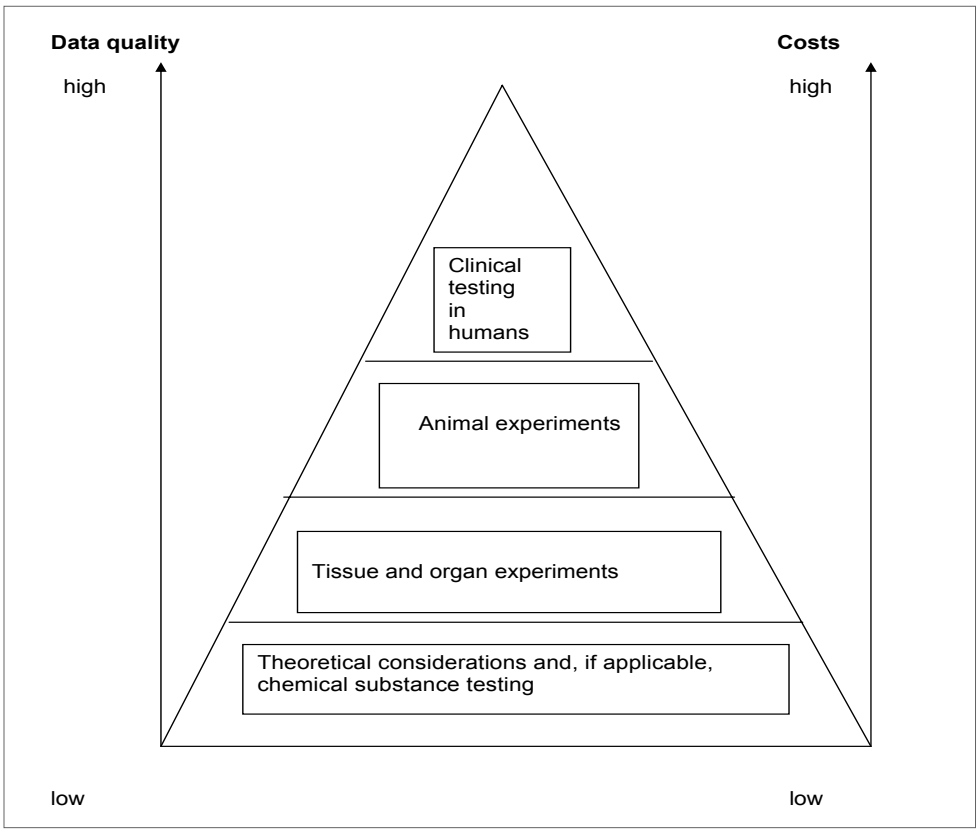
The Contergan scandal proved decisive in paving the way for the first basic medicines directive of what was then the European Economic Community (EEC)[4]. Before clinical trials are conducted in humans, new substances must be tested in at least two animal species (of which one must not be a rodent). "Exactly what has to be done and how is laid down in the ICH guidelines (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use)[5]; studies in rat and rabbit embryos have prevented disasters," says Pfannkuch.

But overall, studies in animal embryos have become less important over the years, explains the toxicologist. "Reproduction toxicity studies are usually not carried out until later phases of drug development, and many substances tend to 'die' along the way before becoming a medicine." Many drug candidates nowadays are also tested, for example, in embryonic stem cells. The most important issue for companies in drug development once they have a product, says Pfannkuch, is that its "efficacy and safety have to be proven in humans."

Whether or not tests are conducted in animal embryos also depends on the diseases for which the medicine is later to be used. "In the case of eye drops to treat glaucoma, for example, reproduction toxicity is often not systematically and comprehensively tested in animal experiments because they are mainly used by elderly people," says Pfannkuch. In the package leaflet, the following caution is then included: "Must not be used in pregnancy, because the potential risk for humans is not known." The situation is quite different when it comes to headaches or sleeping tablets.

Or with medicines for an HIV infection, antipsychotic agents or products that are used, for example, to treat stroke or thrombosis. For example, in the French HIV pregnancy register (the world's largest database for recording possible embryotoxic effects of HIV medicines), a slightly increased rate of neurological malformations was found in babies whose mothers had been treated with the HIV drug efavirenz in pregnancy. Neurological defects had already occurred beforehand in animal models as a result of treatment with this product, but "despite these warnings" the WHO classified the benefit of efavirenz as greater than the damage on the basis of a meta-analysis[6].

An increased rate of premature births and damage to health has also been observed with the use of antipsychotic agents during pregnancy. In experi-



Source: Herbert Büttner, Die Arzneimittelsicherheit bei Humanarzneimitteln, mit besonderer Betrachtung des Einflusses von Krisenfällen auf die Regelsetzung; PhD Thesis, Faculty of Mathematics and Natural Sciences, 2010 (Drug safety in human medicines with particular regard to the impact of crises on regulations)

ments with pregnant rats, Shrikant Gautam and other Indian researchers at the University of Allahabad have now shown a possible cause: the medicine risperidone (an antipsychotic agent) affects not only size and weight, but also the architecture of the placenta and in this way could have a negative impact on the wellbeing of the maturing embryo[7]. Active substances that target the central nervous system often have a low molecular weight, which increases the likelihood of them easily crossing the placental barrier.

No contraceptive method works with 100 % reliability. It is therefore quite possible that the hormones taken for contraceptive purposes may affect the embryo during the first weeks of gestation, because the woman is not yet aware of the pregnancy. Animal experiments are useful for estimating the risk in this area. Because of the different genetic makeup, the results of animal experiments cannot necessarily be extrapolated to humans, write Thomas Rabe from the University of Heidelberg Gynaecology Clinic and other doctors[8]. But together with case reports and epidemiological studies, they nevertheless offer important and indispensable pointers to the possible adverse effects on unborn life of a wide variety of active substances.

Sources:

[1] https://www.nature.com/articles/ncomms15112

[2] https://www.statnews.com/2017/04/25/mechanical-womb-premature-infant/

[3] http://www.sueddeutsche.de/wissen/geburtsmedizin-laemmer-wachsen-in-kuenstlicher-gebaermutter-1.3477748

[4] http://hss.ulb.uni-bonn.de/2010/2163/2163.htm

[5] http://www.ich.org/home.html

[6] http://www.pharmazeutische-zeitung.de/?id=46056

[7] https://www.ncbi.nlm.nih.gov/pubmed/27256515

[8] http://www.kup.at/kup/pdf/11792.pdf

It would be ideal if we could understand the complicated mechanisms of a body without stressful animal experiment. Unfortunately that is not yet possible today. But the dilemma will remain for a long time to come: basic research without experiments in animals would mean abandoning any medical progress. Mice Times aims to explain why and therefore reports on medical success stories that were only possible thanks to animal experiments.

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