1964-1976

Salicylate is a powerful inhibitor of fatty acid release. (Bizzi A et al. Salicylate, a powerful inhibitor of free fatty acid release. Nature 1964; 204: 1205)


For the first time with a new sensitive method it is possible to obtain a map of the distribution of N-acetylaspartic acid in rat brain. (Marcucci F, et al. Distribution of N-acetyl-L-aspartic acid in rat brain. J Neurochem 1966; 13: 1069-1070)


A series of research on drugs affecting aggressiveness of mice is reported. (Valzelli L. Drugs and aggressiveness. Adv Pharmacol 1967; 5: 79-108)


An attempt to quantify cancer dissemination open the possibility to detect antimetastatic agents. (Garattini S. Summary of informal discussion on model systems. Cancer Res 1969; 29: 2339-2344)


Discovery of the mechanism of action regarding the anorectic activity of fenfluramine.  

*Samarin R, et al.*  
The effects of selective lesioning of brain serotonin or catecholamine containing neurones on the anorectic activity of fenfluramine and amphetamine.  
*Eur J Pharmacol* 1972; 19: 318-322

Administration of L-dopa, an antiparkinson drug at doses inducing its increase in brain, induces a decrease of 5HT which is probably related to competition to the transport of tryptophan across the blood-brain barrier (*Algeri S, et al.*  
Effects of L-Dopa administration on the serotonergic system in rat brain: Correlation between levels of L-Dopa accumulated in the brain and depletion of serotonin and tryptophan.  
*Eur J Pharmacol* 1974; 27: 191-197)

An extensive study indicates an increase of brain acetylcholine after administration of diazepam, an effect not related to levels of choline or to the enzymes responsible for the synthesis and metabolism of acetylcholine. The effect of ACH has been investigated in relation to different species, brain areas and presence of active metabolites of diazepam in brain (*Bianchi S, et al.* Dopaminergic-cholinergic interaction in the striatum decrease in rat striatal acetylcholine (ACh) levels by dopaminergic and cholinergic antagonists.  
Action of the benzodiazepines on the cholinergic system In: Mechanism of action of benzodiazepines.  
*Raven Press, New York 1975*

Biochemical data on 5HT and NA show an interaction between the ventral raphe and the locus coeruleus in rat’s brain (*Kostowski W, et al.*  
Biochemical aspects of the interaction between midbrain raphe and locus coeruleus in the rat.  
*Brain Res* 1974; 82: 178-182)

Isolation of male, but not female, mice and rats induces aggressiveness with a number of other behavioral parameters. Biochemical changes include decrease of 5HT turnover, decrease of N-acetyl-L-aspartic and decreased cholinergic transmission. The aggressive effect is antagonized by benzodiazepines and antipsychotic drugs (*Valzelli L.* Aggressiveness by isolation in rodents In: Determinants and origins of aggressive behavior.  
*Mouton Publ., The Hague 1974*

Pioneer studies in experimental metastases have allowed to detect different concentrations of drugs in primary tumors vs metabolites (*Spreafico F et al.*  
Selective antimetastatic treatment-current status and future prospects.  
*Cancer Treat Rev* 1974; 1: 239-250)

Racemic fenfluramine, a drug decreasing appetite, is more effective than its enantiomers or metabolite (norfenfluramine) in releasing serotonin and inhibiting its re-uptake in platelets in vitro. The stronger release that re-uptake of serotonin explain the decrease of serotonin concentration in platelets and brain (*Buczko W, et al.*  
Effect of fenfluramine on 5-hydroxytryptamine uptake and release by rat blood platelets.  
*Br J Pharmacol* 1975; 53: 563-568)

The absorption of L-Dopa is impaired by anticholinergic agents in rats, normal subjects and Parkisonian patients (*Algeri S, et al.*  
Effect of anticholinergic drugs on gastrointestinal absorption of L-DOPA in rats and in man.  
*Eur J Pharmacol* 1976; 35: 293-299)

Experimental attemps are made to relate pharmacokinetic parameters to pharmacodynamic variability in patients treated with psychotropics or anticancer drugs (*Garattini S.* Variability of psychotrophic drug response.  
The contribution of biochemical pharmacology to its elucidation In: Advances in the drug therapy of mental illness  
Metastasizing capacity of tumour cells from spontaneous metastases of transplanted murine tumours.  
*Br J Cancer* 1980; 42: 462-472)

Pioneer work shows that distribution of anticancer agents is heterogenous in different parts of the tumor being higher on the surface and much lower in the center (Donelli M G, et al Importance of the presence of necrosis in studying drug distribution within the tumor tissue. Eur J Drug Metab Pharmacokinet 1977; 2: 63-67)

Venous tissues of renal failure patients show higher prostacyclin level in respect to control subjects. This may explain the very prolonged bleeding time of these patients (Remuzzi G, et al. Prostacyclin-like activity and bleeding in renal failure. Lancet 1977; 2: 1195-1197)


The Mario Negri Institute’s analytical capacities have enabled it to identify the 3,4,7,8-tetrachlorodibenzo-dioxin as the toxic outcome of the Seveso event in 1976. Monitoring the area at the time allowed the rapid transfer of people to uncontaminated areas.(Adamoli P et al. Analysis of 2,3,7,8-tetrachlorodibenzo-para-dioxin in the Seveso area. Ecological Bulletin 1978; 27: 31-38)

The Mario Negri Institute has significantly contributed to the creation of the Italian National Health Service (NHS) , to promoting laws against smoking, to revision of the Formulary of drugs reimbursed by the NHS and to establishing the European law on orphan drugs.


Patients with advanced ovarian tumors show lower level of “killer cells” in respects to control patients. Chemotherapy is proportionally more active in patients with high levels of K cells (Mantovani A, et al. K cell activity in ovarian cancer patients given chemotherapy. Eur J Cancer 1979; 15: 797-802)

Several experimental studies in vivo indicate that anthracycline drugs in addiction to their cytotoxicity exert an antitumoral activity by enhancing immunological activity of macrophages (Mantovani A, et al. The role of host defense mechanisms in the antitumor activity of adriamycin and daunomycin in mice. J Natl Cancer Inst 1979; 63: 61-66)

TCCD (dioxin) induces in mice a profound immunosuppression on primary and secondary humoral response to T dependent and T independent antigens (Vecchi A et al. The effect of acute administration of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on humoral antibody production and cell-mediated activities in mice. Arch Toxicol 1980; s.4: 163-165)

Treatment with progestogens does not protect pregnant women from spontaneous abortion (Tognoni G et al. Progestagens in threatened abortion. Lancet 1980; 2: 1242-1243)


A number of experimental and clinical studies have been performed on monosodium glutamate. All these data contradict the hypothesis that this amino acid is responsible of asthmatic attacks and the Chinese restaurant syndrome (Garattini S. 'Chinese-restaurant asthma'. N Engl J Med 1982; 306: 1181)


Several studies indicate at the experimental and clinical level an important role for serotonin in suppressing feeding (Samanin R. Drugs affecting serotonin and feeding. In: Biochemical pharmacology of obesity. Elsevier, Amsterdam 1983)

The Mario Negri Institute was one of the founders and supporters of clinical pharmacology. Over the years at the Institute a number of researchers from around the world have been formed in the discipline, and contributed to its implementation and development to a more appropriate use of drugs (Bonati M, et al. Has clinical pharmacology lost its way? Lancet 1984; 1 : 556-558)

The risk of epithelial ovarian cancer in subjects utilizing combination anti-contraceptives is reduced by 40% in Italian population (La Vecchia C, et al. Oral contraceptive use and the risk of epithelial ovarian cancer. Br J Cancer 1984; 50: 31-34)
Tricyclic and “atypical” antidepressant drugs are supposed to act as inhibitors of monoamine uptake. This view is criticized on the basis of experimental findings showing other kind of activities including among others: decrease of beta-adrenergic receptors, increased sensitivity of alpha 1-adrenoreceptors, down regulation of 5HT2 receptors, subsensitivity of pre-synaptic dopamine receptors and enhanced dopamine functions (Garattini S, et al. Drugs: Guide and caveats to explanatory and descriptive approaches. I. A critical evaluation of the current status of antidepressant drugs. J Psychiatr Res 1984; 18: 373-390).


1987-1996

The GISSI studies have shown for the first time that a fibrinolytic agent can prevent mortality in 20% of patients with acute myocardial infarction (50% if treatment starts within three hours from infarction). (GISSI et al. Long-term effects of intravenous thrombolysis in acute myocardial infarction: Final report of the GISSI study. Lancet 1987; 2: 871-874)

Further studies have shown protective effect of nitrites, ACE inhibitors and aspirin on myocardial infarction. (ISIS-2, et al. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. Lancet 1988; 2: 349-360)


First demonstration that the human placenta expresses the endothelin gene and that the corresponding protein is excreted in the urine in increasing amounts over the course of normal pregnancy (Benigni A, et al. Human placenta expresses the endothelin gene and the corresponding protein is excreted in the urine in increasing amounts during the course of normal pregnancy. Am J Obstet Gynecol 1991;164:844-848).


Therapeutic formularies, essential drugs, drug utilization studies characterized much of the activity of the Institute in the knowledge that this is a need for developing and a challenge for the developed countries. (Tognoni G, et al. Therapeutic formularies, essential drugs, drug utilization studies. WHO Reg Publ Eur Ser 1993; 45: 43-53)


Intensive rather than traditional monitoring of patients with mammary cancer after surgery does not influence their survival. (GIVIO, Impact of follow-up testing on survival and health-related quality of life in breast cancer patients. A multicenter randomized controlled trial. JAMA 1994; 271: 1587-1592)


1997-2006


The Mario Negri Institute has largely contributed in its many years to the development of pharmacokinetics, introducing new analytical techniques such as gas and liquid chromatography combined or not with mass spectrometry. (Sottani C, et al. Structural characterization of mono- and dihydroxylated metabolites of paclitaxel in rat bile using liquid chromatography/ion spray tandem mass spectrometry. Rapid Commun Mass Spectrom 1997; 11: 1025-1032)
Demonstration of the renal toxicity of proteins on proximal tubule cells showing that excess proteins induce proximal tubular cells to acquire an inflammatory phenotype through NF-kB activation. (Zoja C, et al. Protein overload stimulates RANTES production by proximal tubular cells depending on NF-kB activation. Kidney Int 1998; 53:1608-1615)


Demonstration that angiotensin converting enzyme inhibition limits proteinuria and prevents the glomerular-tubular disconnection, a protective effect not shared by calcium antagonist (Benigni A, et al. ACE inhibition prevents glomerular-tubule disconnection and atrophy in passive Heymann nephritis, an effect not observed with a calcium antagonist. Am J Pathol 2001;159:1743-1750).


Valsartan significantly reduces the combined end point of mortality and morbidity and improves clinical signs and symptoms in patients with heart failure, when added to prescribed therapy. However, the post hoc observation of an adverse effect on mortality and morbidity in the subgroup receiving valsartan, an ACE inhibitor, and a beta-blocker raises concern about the potential safety of this specific combination.(Cohn J N, et al. A randomized trial of the angiotensin-receptor blocker Valsartan in chronic heart failure. N Engl J Med 2001; 345: 1667-1675)


Special attention was given to activities involving countries in the south of the world both training people from limited resources countries and setting up initiatives aimed at developing greater equity and appropriateness of care in needy countries. (Pandolfini C, et al. Regulatory assessment of new drugs in developing countries. Lancet 2003; 362 : 249-250)

The first functional characterization of a CFH mutation associated with atypical hemolytic uremic syndrome demonstrated a selective impaired complement regulation at endothelial cell level. (Manuelian T, et al. Mutations in factor H reduce binding affinity to C3b and heparin and surface attachment to endothelial cells in hemolytic uremic syndrome. J Clin Invest 2003; 111: 1181-90)


A technology has been developed to measure in slurry and water the amount of drugs of abuse consumed in a given area. Consumption patterns can therefore be followed during days and even years, and new drugs of abuse can be detected. This offers also a simple means of assessing the effect of campaigns to reduce the use of recreational drugs. (Castiglioni S, et al. Identification and measurement of illicit drugs and their metabolites in urban wastewater by liquid chromatography. Tandem mass spectrometry. Anal Chem 2006; 78: 8421-8429)


2007-2016


Ingredients of food that help protect against various tumors have been characterized. (Rossi M, et al. Flavonoids and the risk of oral and pharyngeal cancer: A case-control study from Italy. Cancer Epidemiol Biomarkers Prev 2007; 16: 1621-1625)


Identification of FN1 mutations as cause of 40% of cases of glomerulopathy with fibronectin deposits and characterization of their functional consequences. (Castelletti F, et al. Mutations in FN1 cause glomerulopathy with fibronectin deposits. Proc Natl Acad Sci USA 2008; 105:2538-43)


Demonstration that knocking out angiotensin II type 1 receptor prolongs survival of mice, through attenuation of oxidative stress and overexpression of prosurvival genes. (Benigni A, et al. Disruption of the Ang II type 1 receptor promotes longevity in mice. J Clin Invest 2009; 119:524-530)


Old people’s kidneys of can be used for transplantation (one or both) in old people with renal failure. (Rigotti P, et al. Outcome of renal transplantation from very old donors. N Engl J Med 2009; 360: 1464-1465)


Oligomers of β-amyloid are toxic in vitro and reduce memory in animals, showing that the neuronal toxicity of β-amyloid is not related solely to the presence of plaques. On this basis several drugs have proved able to antagonize the toxicity of β-amyloid oligomers with different mechanisms. (Balducci C, et al. Synthetic amyloid-beta-oligomers impair long-term memory independently of cellular prion protein. Proc Natl Acad Sci USA 2010; 107: 2295-2300)

Trabectedine, a drug derived from marine organisms, essentially developed at “Mario Negri” labs, is active in some types of ovarian cancer and soft sarcomas. (for example Germano G, et al. Antitumor and anti-inflammatory effects of trabectedin on human mixoid liposarcoma cells. Cancer Res 2010; 70: 2235-2244)


The malignancy of ovarian cancer can be predicted from the level of miRNA 200c with an inverse relationship. This allows to determine the intensity of the chemotherapy. (Marchini S, et al. Association between miR-200c and the survival of patients with stage I epithelial ovarian cancer: a retrospective study of two independent tumour tissue collections. Lancet Oncol 2011; 12: 273-285)


Experimental studies on stroke show activation of the complement cascade as well as an increase of the mannose binding protein (MBP). Effective drugs have been developed.(Frigerio F, et al.Long-lasting pro-ictogenic effects induced in vivo by rat brain exposure to serum albumin in the absence of concomitant pathology. Epilepsia 2012; 53: 1887-1897)
Various epidemiological studies have contributed to the quantification of the excess risk of cancer in relation to type 2 diabetes mellitus (Bosetti C, et al. Diabetes mellitus and cancer risk in a network of case-control studies. Nutr Cancer 2012; 64: 643-651)


A large RCT involving about 800 Italian practitioners showed no benefit of omega-3 fatty acids on cardiovascular mortality. These products were included in the list of drugs reimbursed by the NHS. (Risk and Prevention Study Collaborative Group et al. n3 Fatty acids in patients with multiple cardiovascular risk factors. N Engl J Med 2013; 368: 1800-1808)

A RCT on non-small cell lung cancer found that erlotinib, an expensive drug, is inferior to the generic drug docetaxel. (Garassino M C, et al. Erlotinib versus docetaxel as second-line treatment of patients with advanced non-small-cell lung cancer and wild-type EGFR tumours (TAILOR): a randomised controlled trial. Lancet Oncol 2013; 14: 981-988)


Epidemiological studies conducted in Italy have identified a spectrum of tumors associated with smoking. Ingredients of food that help protect against various tumors have also been characterized. (Gallus S, et al. Smoking prevalence in Italy 2011 and 2012, with a focus on hand-rolled cigarettes. Prev Med 2013; 56: 314-318)

Finding of a gene-based communication mechanism between BM-MSC and tubular cells based on the release of exosomes from BM-MS which exert renoprotective effects in tubular cells. (Tomasoni S, et al. Transfer of growth factor receptor mRNA via exosomes unravels the regenerative effect of mesenchymal stem cells. Stem Cells Dev 2013; 22; 772-780)

Pharmacokinetic studies have shown that anticancer agents are not distributed uniformly in tumors because they fail to reach several areas at the center of the tumor. This shows that certain cancer cells that proliferate seem to be resistant but in fact they have not come into contact with the drug. (Morosi L, et al. Determination of paclitaxel distribution in solid tumors by nano-particle assisted laser desorption ionization mass spectrometry imaging. PLoS One 2013; 8: e72532)

The Mario Negri Institute has made available “Intercheck”, a platform concerning the potential interactions between drugs and between drugs and food or herbal extracts. (Ghibelli S, et al. Prevention of inappropriate prescribing in hospitalized older patients using a computerized prescription support system (INTERcheck ®). Drugs Aging 2013; 30: 821-828)


Discovery of a specific and sensitive test to disclose complement activation at endothelial cell level in atypical hemolytic uremic syndrome and to monitor the efficacy of anti-complement therapy. (Noris M, et al. Dynamics of complement activation in aHUS and how to monitor eculizumab therapy. Blood 2014; 124:1715-1726)


Through Italian and European cross-sectional studies we have shown that the increase in tobacco taxation is the main strategy for tobacco control. (Gallus S, et al Pricing Policies And Control of Tobacco in Europe (PPACTE) project: cross-national comparison of smoking prevalence in 18. European countries. Eur J Cancer Prev 2014; 23: 177-185 ).

To ensure a better mother, child, and adolescent well-being by undertaking interdisciplinary and collaborative work in the field was one of the activities of the Institute,, also involving countries of the north and south of the world. Networks of physicians (obstetric-gynecologists, neonatologists, pediatricians, and child psychiatrists) and of parents were set up, and maintained in the years. One of the main achievements was the first ever performed RCT involving family pediatricians as investigators, the results of which showed the scant effectiveness of inhaled steroids in preventing viral wheezing: a wide improper practice in Italian children (Clavenna A, et al. Effectiveness of nebulized beclomethasone in preventing viral wheezing: an RCT. Pediatrics 2014 ; 133 : e505-e512)

We showed that women treated with trastuzumab-based adjuvant regimen for HER2-positive early breast cancer in clinical practice, have a survival rate within the fourth year of follow-up (89.4%) consistent with estimates from clinical trials. Regimens lasting < 6 months resulted in a worse prognosis (Bonifazi M, et al. Long term survival of HER2-positive early breast cancer treated with trastuzumab-based adjuvant regimen: a large cohort study from clinical practice. Breast 2014; 23: 573-578)

Demonstration that bone marrow-derived mesenchymal stem cells (MSC) exposed to cell-free extracts can be directly reprogrammed into functional renal cells able to integrate into self-forming kidney tissue and to generate tubular structure. (Papadimou E, et al. Direct reprogramming of human bone marrow stromal cells into functional renal cells using cell-free extracts. Stem Cell Reports 2015; 4: 685-698)


Discovery of Sirt3 dysregulation as a critical determinant in skeletal muscle insulin resistance induced by Angiotensin II via mitochondrial abnormalities and excessive ROS production (Macconi D, et al. Sirtuin3 Dysfunction Is the Key Determinant of Skeletal Muscle Insulin Resistance by Angiotensin II. PLoS One 2015; 10: e0127172,).


Comparative studies on schizophrenic patients show that a new agent, aripiprazole, is no better than olanzapine and haloperidol. (Parabiaghi A, et al. Metabolic syndrome and drug discontinuation in schizophrenia: a randomized trial comparing aripiprazole olanzapine and haloperidol. Acta Psychiatr Scand 2016; 133: 63-75)


Construction of renal organoids using human amniotic fluid stem cells that were able to become vascularized upon transplantation, formed highly specialized kidney cells, and exerted kidney-specific functions (Xinaris C, et al. Functional human podocytes generated in organoids from amniotic fluid stem cells. J Am Soc Nephrol 2016; 27: 1400-1411)

Definition of the genetic structure and function of molybdoflavoproteins (aldehyde oxidases and xanthine oxidoreductase), a family of enzymes involved in the catabolism of purines and in drug metabolism. (Terao M, et al. Structure and function of mammalian aldehyde oxidases. Arch Toxicol 2016; 90: 753-780)


In press


- In the last 10 years, 2006-2016, the impact factor of 5386 papers is ± 5.76 of which 328 papers have been produced an impact factor > 10 and 13 papers have achieved the cover of the majors scientific journals in the world
- 1100 papers of divulgence have been published in the last ten years
- 257 books have been written by the Institute researchers

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