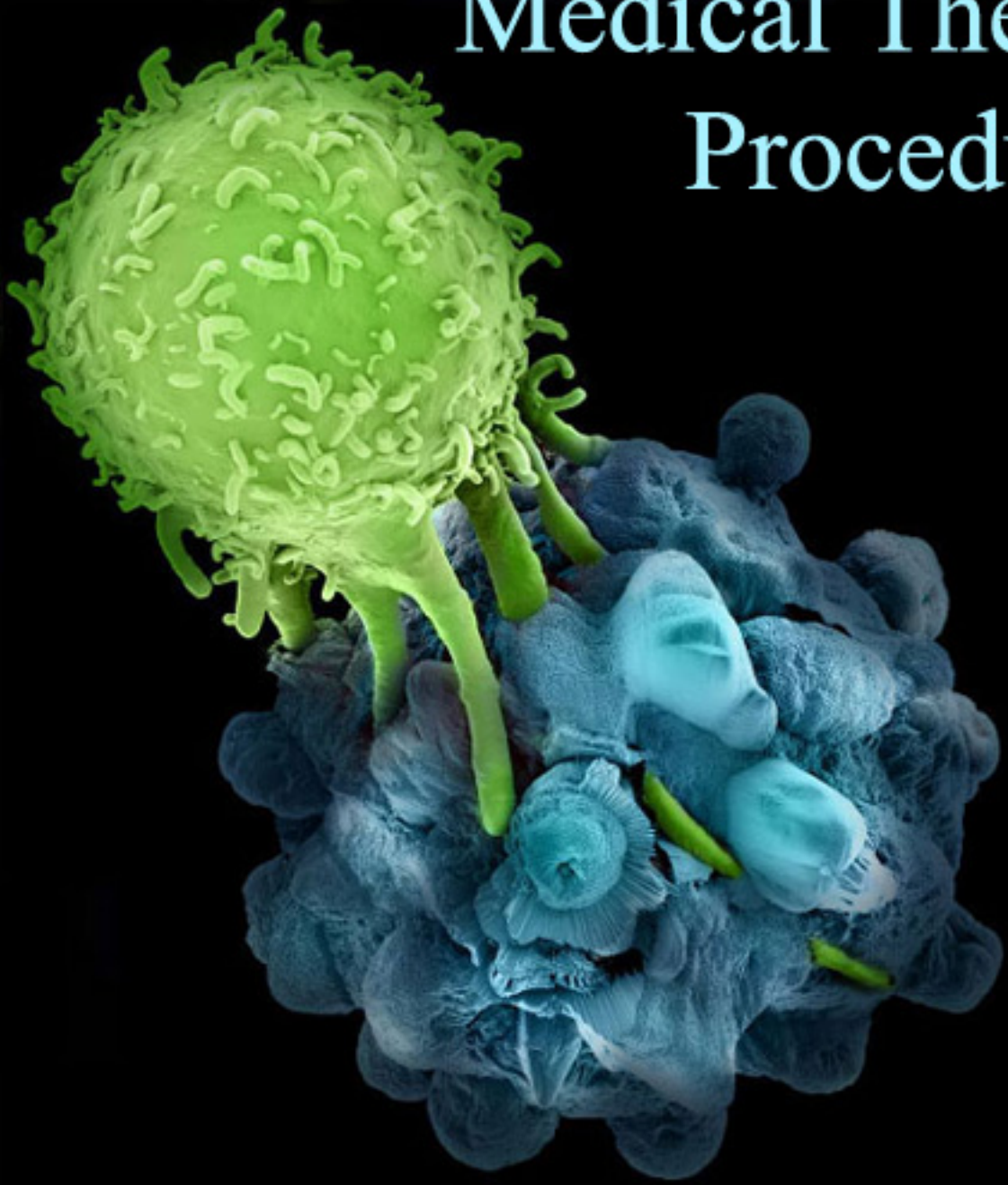
Medical Therapeutic Procedures



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Chapter 1

Hemofiltration

In medicine, **hemofiltration**, also **haemofiltration**, is a renal replacement therapy similar to hemodialysis which is used almost exclusively in the intensive care setting. Thus, it is almost always used for acute renal failure. It is a *slow continuous* therapy in which sessions usually last between 12 to 24 hours and are usually performed daily. During hemofiltration, a patient's blood is passed through a set of tubing (a *filtration circuit*) via a machine to a semipermeable membrane (the *filter*) where waste products and water are removed. Replacement fluid is added and the blood is returned to the patient.

The Principle of Hemofiltration

As in dialysis, in hemofiltration one achieves movement of solutes across a semi-permeable membrane. However, solute movement with hemofiltration is governed by convection rather than by diffusion. With hemofiltration, dialysate is not used. Instead, a positive hydrostatic pressure drives water and solutes across the filter membrane from the blood compartment to the filtrate compartment, from which it is drained. Solutes, both small and large, get dragged through the membrane at a similar rate by the flow of water that has been engineered by the hydrostatic pressure. So convection overcomes the reduced removal rate of larger solutes (due to their slow speed of diffusion) seen in hemodialysis.

Replacement fluid composition

An isotonic replacement fluid is added to the blood to replace fluid volume and electrolytes. The replacement fluid must be of high purity, because it is infused directly into the blood line of the extracorporeal circuit. The replacement hemofiltration fluid usually contains lactate or acetate as a bicarbonate-generating base, or bicarbonate itself. Use of lactate can occasionally be problematic in patients with lactic acidosis or with severe liver disease, because in such cases the conversion of lactate to bicarbonate can be impaired. In such patients use of bicarbonate as a base is preferred.

Hemodiafiltration

Hemofiltration is sometimes used in combination with hemodialysis, when it is termed hemodiafiltration. Blood is pumped through the blood compartment of a high flux dialyzer, and a high rate of ultrafiltration is used, so there is a high rate of movement of water and solutes from blood to dialysate that must be replaced by substitution fluid that is infused directly into the blood line. However, dialysis solution is also run through the dialysate compartment of the dialyzer. The combination is theoretically useful because it results in good removal of both large and small molecular weight solutes.

Intermittent vs. continuous modes of therapy

These treatments can be given intermittently, or continuously. The latter is usually done in an intensive care unit setting.

On-line intermittent hemofiltration (IHF) or hemodiafiltration (IHDF)

Either of these treatments can be given in outpatient dialysis units, three or more times a week, usually 3-5 hours per treatment. IHDF is used almost exclusively, with only a few centers using IHF. With both IHF or IHDF, the substitution fluid is prepared on-line from dialysis solution by running dialysis solution through a set of two membranes to purify it before infusing it directly into the blood line. In the United States, regulatory agencies have not yet approved on-line creation of substitution fluid because of concerns about its purity. For this reason, hemodiafiltration is almost never used in an outpatient setting in the United States as of 2007. Use of sterile, pre-packaged substitution fluid would be cost-prohibitive in the current economic environment.

Continuous hemofiltration (CHF) or hemodiafiltration (CHDF)

Hemofiltration is most commonly used in an intensive care unit setting, where it is either given as 8-12 hours treatments, so called SLEF (slow extended hemofiltration), or as CHF (continuous hemofiltration also sometimes called continuous veno-venous hemofiltration (CVVH)) or Continuous Renal Replacement Therapy (CRRT). Hemodiafiltration (SLED-F or CHDF or CVVHDF) also is widely used in this fashion. In the United States, the substitution fluid used in CHF or CHDF is commercially prepared, prepackaged, and sterile (or sometimes is prepared in the local hospital pharmacy), avoiding regulatory issues of on-line creation of replacement fluid from dialysis solution.

With slow continuous therapies, the blood flow rates are usually in the range of 100-200 ml/min, and access is usually achieved through a central venous catheter placed in one of the large central veins. In such cases a blood pump is used to drive blood flow through the filter. Native access for hemodialysis (eg AV fistulas or grafts) are unsuitable for CHF because the prolonged residence of the access needles required might damage such accesses.

Is on-line intermittent hemodiafiltration (IHDF) better than regular hemodialysis?

There is controversy about whether intermittent on-line hemodiafiltration (IHDF) gives better results than hemodialysis in an outpatient setting. In Europe, several observational studies have compared outcomes in patients getting dialysis with those getting IHDF. These have suggested a lower mortality rate and other favorable outcomes in patients getting IHDF vs. those getting ordinary hemodialysis. However, the issue is not settled at this time, because the required randomized controlled clinical trials have not been done. Another problem has been that in several of the trials done, IHDF was compared to dialysis using low-flux (small pore) membranes, and the benefit found may have been due more to the use of a high-flux membrane than to the addition of convective transport (filtration) to dialysis. A recent Cochrane database review of available trials could not find a definite benefit of either IHF or IHDF vs. hemodialysis in terms of outcomes.

Chapter 2

Plasmapheresis

Plasmapheresis (from the Greek *πλάσμα* - *plasma*, something molded, and *ἀφαίρεσις* - *aphairesis*, taking away) is the removal, treatment, and return of (components of) blood plasma from blood circulation. It is thus an extracorporeal therapy (a medical procedure which is performed outside the body). The method can also be used to collect plasma for further manufacturing into a variety of medications.

The procedure is used to treat a variety of disorders, including those of the immune system, such as Myasthenia gravis Guillain-Barré syndrome, lupus, and thrombotic thrombocytopenic purpura. Dr. D. J. Wallace states that Michael Rubinstein was the first person to use plasmapheresis to treat an immune-related disorder when he "saved the life of an adolescent boy with thrombotic thrombocytopenic purpura (TTP) at the old Cedars of Lebanon Hospital in Los Angeles in 1959". Also according to Wallace, the modern plasmapheresis process itself originated in the "[U.S.] National Cancer Institute between 1963 and 1968, [where] investigators drew upon an old dairy creamer separation technology first used in 1878 and refined by Edwin Cohn's centrifuge marketed in 1953.

As therapy

During plasmapheresis, blood is initially taken out of the body through a needle or previously implanted catheter. Plasma is then removed from the blood by a cell separator. Three procedures are commonly used to separate the plasma from the blood cells:

- Discontinuous flow centrifugation: One venous catheter line is required. Typically, a 300 ml batch of blood is removed at a time and centrifuged to separate plasma from blood cells.
- Continuous flow centrifugation: Two venous lines are used. This method requires slightly less blood volume to be out of the body at any one time as it is able to continuously spin out plasma.
- Plasma filtration: Two venous lines are used. The plasma is filtered using standard hemodialysis equipment. This continuous process requires less than 100 ml of blood to be outside the body at one time.

Each method has its advantages and disadvantages. After plasma separation, the blood cells are returned to the person undergoing treatment, while the plasma, which contains the antibodies, is first treated and then returned to the patient in traditional plasmapheresis. (In plasma exchange, the removed plasma is discarded and the patient receives replacement donor plasma, albumin, or a combination of albumin and saline (usually 70% albumin and 30% saline). Rarely, other replacement fluids, such as hydroxyethyl starch, may be used in individuals who object to blood transfusion but these are rarely used due to severe side-effects. Medication to keep the blood from clotting (an anticoagulant) is given to the patient during the procedure. Plasmapheresis is used as a therapy in particular diseases. It is an uncommon treatment in the United States, but it is more common in Europe and particularly Japan.

An important use of plasmapheresis is in the therapy of autoimmune disorders, where the rapid removal of disease-causing autoantibodies from the circulation is required in addition to other medical therapy. It is important to note that plasma exchange therapy in and of itself is useful to temper the disease process, where simultaneous medical and immunosuppressive therapy is required for long-term management. Plasma exchange offers the quickest short-term answer to removing harmful autoantibodies; however, the production of autoantibodies by the immune system must also be suppressed, usually by the use of medications such as prednisone, cyclophosphamide, cyclosporine, mycophenolate mofetil, rituximab or a mixture of these.

Other uses are the removal of blood proteins where these are overly abundant and cause hyperviscosity syndrome.

Examples of diseases that can be treated with plasmapheresis:

- Guillain-Barré syndrome
- Chronic inflammatory demyelinating polyneuropathy
- Goodpasture's syndrome
- Hyperviscosity syndromes:
    - Cryoglobulinemia
    - Paraproteinemia
    - Waldenström macroglobulinemia
- Myasthenia gravis
- Thrombotic thrombocytopenic purpura (TTP)/hemolytic uremic syndrome
- Wegener's granulomatosis
- Lambert-Eaton Syndrome
- Antiphospholipid Antibody Syndrome (APS or APLS)
- Microscopic polyangiitis
- Recurrent focal and segmental glomerulosclerosis in the transplanted kidney
- HELLP syndrome
- Refsum disease
- Behcet syndrome
- HIV-related neuropathy
- Graves' disease in infants and neonates

- Pemphigus vulgaris
- Multiple sclerosis
- Rhabdomyolysis

Complications of plasmapheresis therapy

Though plasmapheresis is helpful in certain medical conditions, like any other therapy, there are potential risks and complications. Insertion of a rather large intravenous catheter can lead to bleeding, lung puncture (depending on the site of catheter insertion), and, if the catheter is left in too long, it can get infected.

Aside from placing the catheter, the procedure itself has complications. When patient blood is outside of the body passing through the plasmapheresis machine, the blood has a tendency to clot. To reduce this tendency, in one common protocol, citrate is infused while the blood is running through the circuit. Citrate binds to calcium in the blood, calcium being essential for blood to clot. Citrate is very effective in preventing blood from clotting; however, its use can lead to life-threateningly low calcium levels. This can be detected using the Chvostek's sign or Trousseau's sign. To prevent this complication, calcium is infused intravenously while the patient is undergoing the plasmapheresis; in addition, calcium supplementation by mouth may also be given.

Other complications include:

- Potential exposure to blood products, with risk of transfusion reactions or transfusion transmitted diseases
- Suppression of the patient's immune system
- Bleeding or hematoma from needle placement

As a manufacturing process

Donating plasma is similar in many ways to whole blood donation, though the end product is used for different purposes. Most plasmapheresis is for fractionation into other products, other blood donations are transfused with relatively minor modifications. Plasma that is collected solely for further manufacturing is called Source Plasma.

Plasma donors undergo a screening process to ensure both the donor's safety and the safety of the collected product. Factors monitored include blood pressure, pulse, temperature, total protein, protein electrophoresis, health history screening similar to that for whole blood, as well as an annual physical exam with a licensed physician or an approved physician substitute under the supervision of the physician. Donors are screened at each donation for viral diseases that can be transmitted by blood, sometimes by multiple methods. For example, donors are tested for HIV by EIA, which will show if they have ever been exposed to the disease, as well as by nucleic acid methods (PCR or similar) to rule out recent infections that might be missed by the EIA test. Industry standards require at least two sets of negative test results before the collected plasma is

used for injectable products. The plasma is also treated in processing multiple times to inactivate any virus that was undetected during the screening process.

Plasma donors are typically paid cash for their donations, though this is not universal. For example, donors in the UK, Australia and New Zealand are not given financial incentives. Since the products are heavily processed and treated to remove infectious agents, the higher risk is considered acceptable. Standards for donating plasma are set by national regulatory agencies such as the U.S. Food and Drug Administration (FDA), the European Union, and by a professional organization, the Plasma Protein Therapeutics Association (or PPTA), which audits and accredits collection facilities. A National Donor Deferral Registry (NDDR) is also maintained by the PPTA for use in keeping donors with prior positive test results from donating at any facility.

Almost all plasmapheresis in the US is performed by automated methods such as the Plasma Collection System (PCS2) made by Haemonetics or the Autopheresis-C (Auto-C) made by Fenwal, a division of Baxter International. In some cases, automated plasmapheresis is used to collect plasma products like Fresh frozen plasma for direct transfusion purposes, often at the same time as plateletpheresis.

Manual method

> For the manual method, approximately the same as a whole blood donation is collected from the donor. The collected blood is then separated by centrifuge machines in separate rooms, the plasma is pressed out of the collection set into a satellite container, and the red blood cells are returned to the donor. Since returning red cells causes the plasma to be replaced more rapidly by the body, a donor can provide up to a liter of plasma at a time and can donate with only a few days between donations, unlike the 56-day deferral for blood donation. The amount allowed in a donation varies vastly from country to country, but generally does not exceed two donations, each as much as a liter, per 7-day period.

The danger with this method was that if the wrong red blood cells were returned to the donor, a serious and potentially fatal transfusion reaction could occur. Requiring donors to recite their names and ID numbers on returned bags of red cells minimized this risk. This procedure has largely become obsolete in favor of the automated method.

Automated method

> The automated method uses a very similar process. The difference is that the collection, separation, and return are all performed inside a machine which is connected to the donor through a needle placed in the arm, typically the antecubital vein. There is no risk of receiving the wrong red cells. The devices used are very similar to the devices used for therapeutic plasmapheresis, and the potential for citrate toxicity is similar. The potential risks are explained to prospective donors at the first donation, and most donors tolerate the procedure well.

If a significant amount of red blood cells cannot be returned, the donor may not donate for 56 days, just as if they had donated a unit of blood. Depending on the collection system and the operation, the removed plasma may be replaced by saline. The body will typically replace the collected volume within 24 hours, and donors typically donate up to twice a week, though this varies by country.

The collected plasma is promptly frozen at lower than -20 °C (-4 °F) and is typically shipped to a processing facility for fractionation. This process separates the collected plasma into specific components, such as albumin and immunoglobulins, most of which are made into medications for human use. Sometimes the plasma is thawed and transfused as Fresh Frozen Plasma (FFP), much like the plasma from a normal blood donation.

Donors are sometimes immunized against agents such as tetanus or hepatitis B so that their plasma contains the antibodies against the toxin or disease. In other donors, an intentionally incompatible unit of blood is transfused to produce antibodies to the antigens on the red cells. The collected plasma then contains these components, which are used in manufacturing of medications. Donors who are already ill may have their plasma collected for use as a positive control for laboratory testing.

Chapter 3

Cancer Immunotherapy

Cancer immunotherapy is the use of the immune system to reject cancer. The main premise is stimulating the patient's immune system to attack the malignant tumor cells that are responsible for the disease. This can be either through immunization of the patient (eg. by administering a cancer vaccine, such as Dendreon's Provenge), in which case the patient's own immune system is trained to recognize tumor cells as targets to be destroyed, or through the administration of therapeutic antibodies as drugs, in which case the patient's immune system is recruited to destroy tumor cells by the therapeutic antibodies.

Since the immune system responds to the environmental factors it encounters on the basis of discrimination between self and non-self, many kinds of tumor cells that arise as a result of the onset of cancer are more or less tolerated by the patient's own immune system since the tumor cells are essentially the patient's own cells that are growing, dividing and spreading without proper regulatory control.

In spite of this fact, however, many kinds of tumor cells display unusual antigens that are either inappropriate for the cell type and/or its environment, or are only normally present during the organisms' development (e.g. fetal antigens). Examples of such antigens include the glycosphingolipid GD2, a disialoganglioside that is normally only expressed at a significant level on the outer surface membranes of neuronal cells, where its exposure to the immune system is limited by the blood-brain barrier. GD2 is expressed on the surfaces of a wide range of tumor cells including neuroblastoma, medulloblastomas, astrocytomas, melanomas, small-cell lung cancer, osteosarcomas and other soft tissue sarcomas. GD2 is thus a convenient tumor-specific target for immunotherapies.

Other kinds of tumor cells display cell surface receptors that are rare or absent on the surfaces of healthy cells, and which are responsible for activating cellular signal transduction pathways that cause the unregulated growth and division of the tumor cell. Examples include ErbB2, a constitutively active cell surface receptor that is produced at abnormally high levels on the surface of breast cancer tumor cells.

Monoclonal antibody therapy

Antibodies are a key component of the adaptive immune response, playing a central role in both in the recognition of foreign antigens and the stimulation of an immune response to them. It is not surprising therefore, that many immunotherapeutic approaches involve the use of antibodies. The advent of monoclonal antibody technology has made it possible to raise antibodies against specific antigens such as the unusual antigens that are presented on the surfaces of tumors.

A number of therapeutic monoclonal antibodies have been approved for use in humans; approvals mentioned here are by the U.S. Food and Drug Administration (FDA).

Cancer immunotherapy:Monoclonal antibodies

Antibody	Brand name	Approval date	Type	Target	Approved treatment(s)
Alemtuzumab	Campath	2001	humanized	CD52	Chronic lymphocytic leukemia
Bevacizumab	Avastin	2004	humanized	vascular endothelial growth factor	colorectal cancer
Cetuximab	Erbitux	2004	chimeric	epidermal growth factor receptor	colorectal cancer
Gemtuzumab ozogamicin	Mylotarg	2000	humanized	CD33	acute myelogenous leukemia (with calicheamicin)
Ibritumomab tiuxetan	Zevalin	2002	murine	CD20	non-Hodgkin lymphoma (with yttrium-90 or indium-111)
Panitumumab	Vectibix	2006	human	epidermal	colorectal cancer

				growth factor receptor	
Rituximab	Rituxan, Mabthera	1997	chimeric	CD20	non-Hodgkin lymphoma
Trastuzumab	Herceptin	1998	humanized	ErbB2	breast cancer

Alemtuzumab

Alemtuzumab is an anti-CD52 humanized IgG1 monoclonal antibody indicated for the treatment of Chronic lymphocytic leukemia(CLL), the most frequent form of leukaemia in Western countries. The function of CD52 is unknown, but it is found on >95% of peripheral blood lymphocytes and monocytes. Upon binding to CD52, alemtuzumab initiates its cytotoxic effect by complement fixation and antibody-dependent cell-mediated cytotoxicity mechanisms. Alemtuzumab therapy is also indicated for T-prolymphocytic leukaemia (TPPL), for which no standard treatment exists. This is a highly aggressive tumour, with a median survival of 7.5 months.

Bevacizumab

Bevacizumab is a humanized IgG1 monoclonal antibody which binds to and sterically interferes with the vascular endothelial growth factor-A (VEGF-A), preventing receptor activation. A marked increase in VEGF expression is thought to play a role in tumor angiogenesis. Bevacizumab is indicated for colon cancer; but has been applied to numerous other cancers in small scale studies, especially renal cell carcinoma. Results obtained showed that bevacizumab increased the duration of survival, progression-free survival, the rate of response and the duration of response in a statistically relevant manner.

Cetuximab

Cetuximab is a chimeric IgG1 monoclonal antibody which targets the extracellular domain of the epidermal growth factor receptor (EGFR). It functions by competitively inhibiting ligand binding, thereby preventing EGFR activation, and is indicated for the treatment of colorectal cancer. Studies have also been carried out on numerous other malignancies, especially non-small cell lung cancer and head and neck cancer. As a single agent, cetuximab showed a response rate of 10.8% in patients with EGFR overexpressed metastatic colon cancer. Other anti-EGFR monoclonal antibodies in development include: ABX-EGF, hR3, and EMD 72000. Although they hold significant promise for the future, as of yet none of the agents are currently beyond phase I clinical trials.

Gemtuzumab ozogamicin

Gemtuzumab ozogamicin is an "immuno-conjugate" of an anti-CD33 antibody chemically linked to calicheamicin, a cytotoxic agent. It is indicated for the treatment of acute myeloid leukaemia (AML). The patient group most likely to benefit from gemtuzumab is young adults, and trials have reported high complete responses (85%), when combined with intensive chemotherapy. There are minimal side-effects associated with Gemtuzumab therapy.

Rituximab

Rituximab is a chimeric monoclonal antibody specific for CD20. CD20 is widely expressed on B-cells. Although the function of CD20 is relatively unknown it has been suggested that CD20 could play a role in calcium influx across plasma membrane, maintaining intracellular calcium concentration and allowing for the activation of B cells. The exact mode of action of rituximab is also unclear, but it has been found to have a general regulatory effect on the cell cycle and on immune-receptor expression. Experiments involving primates showed that treatment with anti-CD20 reduced peripheral B-cells by 98%, and peripheral lymph node and bone marrow B-cells by up to 95%.

Trastuzumab

Trastuzumab is a monoclonal IgG1 humanized antibody specific for the epidermal growth factor receptor 2 protein (HER2). It received FDA-approval in 1998, and is clinically used for the treatment of breast cancer. The use of Trastuzumab is restricted to patients whose tumours over-express HER-2, as assessed by immunohistochemistry (IHC) and either chromogenic or Fluorescent in situ hybridisation (FISH), as well as numerous PCR-based methodologies.

HER-2 is a member of the epidermal growth factor receptor (EGFR) family of transmembrane tyrosine kinases, and is normally involved in regulation of cell proliferation and differentiation. Amplification or overexpression of HER-2 is present in 25-30% of breast carcinomas and has been associated with aggressive tumour phenotype, poor prognosis, non-responsiveness to hormonal therapy and reduced sensitivity to conventional chemotherapeutic agents.

Radioimmunotherapy

Radioimmunotherapy involves the use of radioactively conjugated murine antibodies against cellular antigens. Most research currently involved their application to lymphomas, as these are highly radio-sensitive malignancies. To limit radiation exposure, murine antibodies were especially chosen, as their high immunogenicity promotes rapid clearance from the body.

Ibritumomab tiuxetan

Ibritumomab tiuxetan is a murine antibody chemically linked to a chelating agent which binds yttrium-90. ^{90}Y is a beta radiator, has a half-life of 64 h and a tissue penetration of 1-5 millimetres. Its use has been investigated, primarily in the treatment of follicular lymphoma.

Tositumomab/iodine (^{131}I) tositumomab regimen

Tositumomab is a murine IgG2a anti-CD20 antibody. Iodine (^{131}I) tositumomab is covalently bound to Iodine 131. ^{131}I emits both beta and gamma radiation, and is broken down rapidly in the body. Clinical trials have established the efficacy of a sequential application of tositumomab and iodine (I) tositumomab in patients with relapsed follicular lymphoma.

Advances in immunotherapy

The development and testing of second generation immunotherapies are already under way. While antibodies targeted to disease-causing antigens can be effective under certain circumstances, in many cases, their efficacy may be limited by other factors. In the case of cancer tumors, the microenvironment is immunosuppressive, allowing even those tumors that present unusual antigens to survive and flourish in spite of the immune response generated by the cancer patient, against his or her own tumor tissue. Certain members of a group of molecules known as cytokines, such as Interleukin-2 also play a key role in modulating the immune response, and have been tried in conjunction with antibodies in order to generate an even more devastating immune response against the tumor. While the therapeutic administration of such cytokines may cause systemic inflammation, resulting in serious side effects and toxicity, a new generation of chimeric molecules consisting of an immune-stimulatory cytokine attached to an antibody that targets the cytokine's activity to a specific environment such as a tumor, are able to generate a very effective yet localized immune response against the tumor tissue, destroying the cancer-causing cells without the unwanted side-effects. A different type of chimeric molecule is an artificial T cell receptor.

The targeted delivery of cytokines by anti-tumor antibodies is one example of using antibodies to delivery payloads rather than simply relying on the antibody to trigger an immune response against the target cell. Another strategy is to deliver a lethal radioactive dose directly to the target cell, which has been utilized in the case of the Zevalin therapeutic. A third strategy is to deliver a lethal chemical dose to the target, as used in the Mylotarg therapeutic. Engineering the antibody-payload pair in such a way that they separate after entry into a cell by endocytosis can potentially increase the efficacy of the payload. One strategy to accomplish this is the use of a disulfide linkage which could be severed by the reducing conditions in the cellular interior. However, recent evidence suggests that the actual intracellular trafficking of the antibody-payload after endocytosis is such to make this strategy not generally applicable. Other potentially useful linkage types include hydrazone and peptide linkages.

Latest research

In 2001, two U.S. based non-profit organizations, the Cancer Research Institute and the Ludwig Institute for Cancer Research, formed the Cancer Vaccine Collaborative, a unique global network of clinical trial sites with special expertise in immunology, built to centrally design and coordinate early-stage clinical trials to be run in parallel in order to identify more quickly the optimal combination of reagents, or vaccine components, necessary for a successful therapeutic cancer vaccine. The Cancer Vaccine Collaborative has to-date (June 2009) completed or is currently running more than 40 clinical trials of different therapeutic cancer vaccines, including 37 phase I, 6 phase II, and 1 fully-randomized phase II clinical trials, and has published more than 130 scientific papers in peer-reviewed journals. Nearly all of these trials featured vaccines targeting various forms of the cancer-testes antigen, NY-ESO-1, a highly-immunogenic, prototypical protein marker limited in expression to a wide variety of cancer types but not in normal tissue, with the exception of the immune-privileged testes. Vaccines tested in Cancer Vaccine Collaborative trials have induced integrated immune responses composed of target-specific antibodies and CD4+ and CD8+ T lymphocytes, all of which are held to be essential for effective long-term control of cancer. Insights from these trials have generated a strong framework for the selection of components that will likely comprise an ideal therapeutic cancer vaccine, including: multiple cancer-antigens in various forms delivered with potent adjuvants and all administered in a prime-boost setting in conjunction with a modulator of cancer immunosuppression.

In June 2008, it was announced that US doctors from the Clinical Research Division led by Cassian Yee at Fred Hutchinson Cancer Research Center in Seattle have for the first time successfully treated a skin cancer patient by using immune cells cloned from his own immune system which were then re-injected into him. The patient, who was suffering from advanced skin cancer, was free from tumours within eight weeks of being injected with billions of his own immune cells in the first case of its kind. Experts say that this case could be a landmark in the treatment of cancer in general. Larger trials are now under way.

More new research is being conducted by Drs. Richard O'Reilly and Michel Sadelain. Drs. O'Reilly and Sadelain have done extensive research at Memorial Sloan-Kettering Cancer Center hospital and are among leaders of the cancer adoptive Immunotherapy field

Topical immunotherapy

Dermatologists use new creams and injections in the management of benign and malignant skin tumors. Topical immunotherapy utilizes an immune enhancement cream (imiquimod) which is an interferon producer causing the patient's own killer T cells to destroy warts, actinic keratoses, basal cell carcinoma, squamous cell carcinoma, cutaneous T cell lymphoma, and Superficial spreading melanoma. Injection immunotherapy uses mumps, candida or trichophytin antigen injections to treat warts (HPV induced tumors).

Natural products

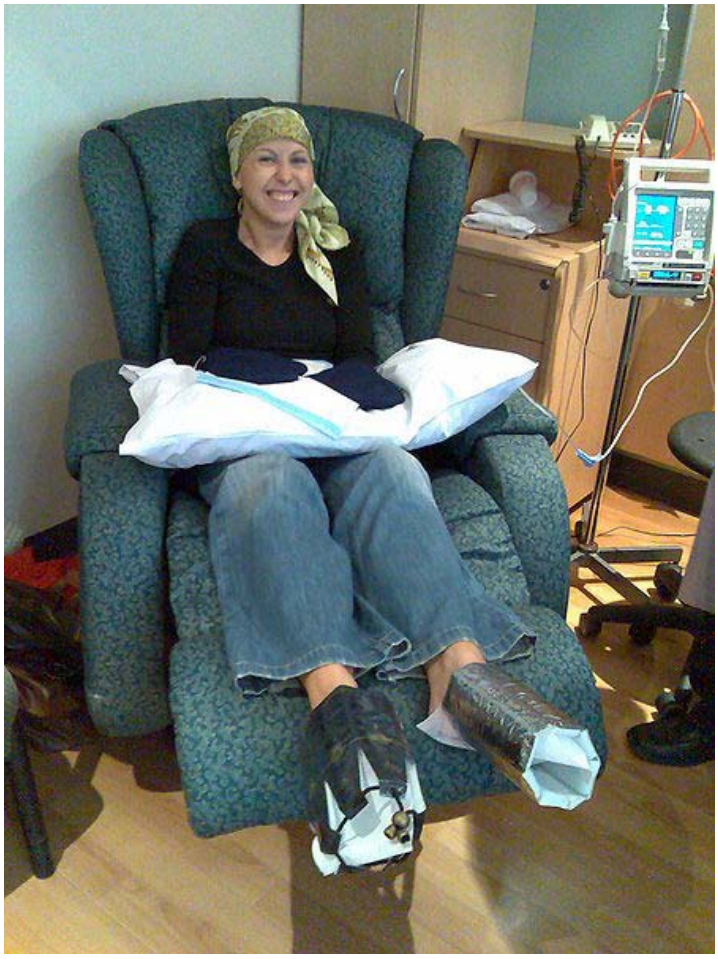
Some types of natural products have shown promise to stimulate the immune system. Research suggests that mushrooms like Reishi and *Agaricus blazei* may be able to stimulate the immune system. Research has shown that *Agaricus blazei* may be a potent stimulator of natural killer cells. *Agaricus blazei* is rich in proteoglucans and beta-glucans, which are potent stimulators of macrophages.

Research ss the compounds in medicinal mushrooms most responsible for up-regulating the immune system and providing an anti-cancer effect, are a diverse collection of polysaccharide compounds, particularly beta-glucans. Beta-glucans are known as "biological response modifiers", and their ability to activate the immune system is well documented. Specifically, beta-glucans stimulate the innate branch of the immune system. Research has shown beta-glucans have the ability to stimulate macrophage, NK cells, T cells, and immune system cytokines. The mechanisms in which beta-glucans stimulate the immune system is only partially understood. One mechanism in which beta-glucans are able to activate the immune system, is by interacting with the Macrophage-1 antigen (CD18) receptor on immune cells.

Highly purified compounds isolated from medicinal mushrooms such as lentinan (isolated from Shiitake), and Polysaccharide-K, (isolated from *Trametes versicolor*), have become incorporated into the health care system of a few countries, such as Japan. Japan's Ministry of Health, Labour and Welfare approved the use of Polysaccharide-K in the 1980s, to stimulate the immune systems of patients undergoing chemotherapy. In Australia, a pharmaceutical based on a mixture of several mycological extracts including lentinan and Polysaccharide-K is sold commercially as MC-S.

Chapter 4

Chemotherapy



A woman being treated with docetaxel chemotherapy for breast cancer. Cold mittens and wine coolers are placed on her hands and feet to reduce harm to her nails.

Chemotherapy, in the most simple sense, is the treatment of an ailment by chemicals especially by killing micro-organisms or cancerous cells. In popular usage, it refers to antineoplastic drugs used to treat cancer or the combination of these drugs into a

cytotoxic standardized treatment regimen. In its non-oncological use, the term may also refer to antibiotics (*antibacterial chemotherapy*). In that sense, the first modern chemotherapeutic agent was arsphenamine, an arsenic compound discovered in 1909 and used to treat syphilis. This was later followed by sulfonamides (sulfa drugs) and penicillin.

Most commonly, chemotherapy acts by killing cells that divide rapidly, one of the main properties of most cancer cells. This means that it also harms cells that divide rapidly under normal circumstances: cells in the bone marrow, digestive tract and hair follicles; this results in the most common side effects of chemotherapy : myelosuppression (decreased production of blood cells, hence also immunosuppression), mucositis (inflammation of the lining of the digestive tract), and alopecia (hair loss).

Other uses of cytostatic chemotherapy agents (including the ones mentioned below) are the treatment of autoimmune diseases such as multiple sclerosis, dermatomyositis, polymyositis, lupus, rheumatoid arthritis and the suppression of transplant rejections.

Newer anticancer drugs act directly against abnormal proteins in cancer cells; this is termed targeted therapy.

History

The use of minerals and plant-based medicines are believed to date back to prehistoric medicine.

The first use of drugs to treat cancer, however, was in the early 20th century, although it was not originally intended for that purpose. Mustard gas was used as a chemical warfare agent during World War I and was studied further during World War II. During a military operation in World War II, a group of people were accidentally exposed to mustard gas and were later found to have very low white blood cell counts. It was reasoned that an agent that damaged the rapidly growing white blood cells might have a similar effect on cancer. Therefore, in the 1940s, several patients with advanced lymphomas (cancers of certain white blood cells) were given the drug by vein, rather than by breathing the irritating gas. Their improvement, although temporary, was remarkable. That experience led researchers to look for other substances that might have similar effects against cancer. As a result, many other drugs have been developed to treat cancer, and drug development since then has exploded into a multibillion-dollar industry, although the principles and limitations of chemotherapy discovered by the early researchers still apply.

Principles

Cancer is the uncontrolled growth of cells coupled with malignant behavior: invasion and metastasis. Cancer is thought to be caused by the interaction between genetic susceptibility and environmental toxins.

In the broad sense, most *chemotherapeutic* drugs work by impairing mitosis (cell division), effectively targeting fast-dividing cells. As these drugs cause damage to cells they are termed *cytotoxic*. Some drugs cause cells to undergo apoptosis (so-called "self programmed cell death").

Scientists have yet to identify specific features of malignant and immune cells that would make them uniquely targetable (barring some recent examples, such as the Philadelphia chromosome as targeted by imatinib). This means that other fast-dividing cells, such as those responsible for hair growth and for replacement of the intestinal epithelium (lining), are also often affected. However, some drugs have a better side effect profile than others, enabling doctors to adjust treatment regimens to the advantage of patients in certain situations.

As chemotherapy affects cell division, tumors with high *growth fractions* (such as acute myelogenous leukemia and the aggressive lymphomas, including Hodgkin's disease) are more sensitive to chemotherapy, as a larger proportion of the targeted cells are undergoing cell division at any time. Malignancies with slower growth rates, such as indolent lymphomas, tend to respond to chemotherapy much more modestly.

Drugs affect "younger" tumors (i.e., more differentiated) more effectively, because mechanisms regulating cell growth are usually still preserved. With succeeding generations of tumor cells, differentiation is typically lost, growth becomes less regulated, and tumors become less responsive to most chemotherapeutic agents. Near the center of some solid tumors, cell division has effectively ceased, making them insensitive to chemotherapy. Another problem with solid tumors is the fact that the chemotherapeutic agent often does not reach the core of the tumor. Solutions to this problem include radiation therapy (both brachytherapy and teletherapy) and surgery.

Over time, cancer cells become more resistant to chemotherapy treatments. Recently, scientists have identified small pumps on the surface of cancer cells that actively move chemotherapy from inside the cell to the outside. Research on p-glycoprotein and other such chemotherapy efflux pumps, is currently ongoing. Medications to inhibit the function of p-glycoprotein are undergoing testing as of June, 2007 to enhance the efficacy of chemotherapy.

Treatment schemes

There are a number of strategies in the administration of chemotherapeutic drugs used today. Chemotherapy may be given with a curative intent or it may aim to prolong life or to palliate symptoms.

Combined modality chemotherapy is the use of drugs with other cancer treatments, such as radiation therapy or surgery. Most cancers are now treated in this way. *Combination chemotherapy* is a similar practice that involves treating a patient with a number of different drugs simultaneously. The drugs differ in their mechanism and side effects. The biggest advantage is minimising the chances of resistance developing to any one agent.

In *neoadjuvant chemotherapy* (*preoperative* treatment) initial chemotherapy is designed to shrink the primary tumour, thereby rendering local therapy (surgery or radiotherapy) less destructive or more effective.

Adjuvant chemotherapy (*post*operative treatment) can be used when there is little evidence of cancer present, but there is risk of recurrence. This can help reduce chances of developing resistance if the tumour does develop. It is also useful in killing any cancerous cells which have spread to other parts of the body. This is often effective as the newly growing tumours are fast-dividing, and therefore very susceptible.

Palliative chemotherapy is given without curative intent, but simply to decrease tumor load and increase life expectancy. For these regimens, a better toxicity profile is generally expected.

All chemotherapy regimens require that the patient be capable of undergoing the treatment. Performance status is often used as a measure to determine whether a patient can receive chemotherapy, or whether dose reduction is required. Because only a fraction of the cells in a tumor die with each treatment (fractional kill), repeated doses must be administered to continue to reduce the size of the tumor. Current chemotherapy regimens apply drug treatment in cycles, with the frequency and duration of treatments limited by toxicity to the patient.

Types

The majority of chemotherapeutic drugs can be divided in to alkylating agents, antimetabolites, anthracyclines, plant alkaloids, topoisomerase inhibitors, and other antitumour agents. All of these drugs affect cell division or DNA synthesis and function in some way.

Some newer agents do not directly interfere with DNA. These include monoclonal antibodies and the new tyrosine kinase inhibitors e.g. *imatinib mesylate* (*Gleevec* or *Glivec*), which directly targets a molecular abnormality in certain types of cancer (chronic myelogenous leukemia, gastrointestinal stromal tumors). These are examples of targeted therapies.

In addition, some drugs that modulate tumor cell behaviour without directly attacking those cells may be used. Hormone treatments fall into this category.

Where available, Anatomical Therapeutic Chemical Classification System codes are provided for the major categories.

Alkylating agents (L01A)

Alkylating agents are so named because of their ability to alkylate many nucleophilic functional groups under conditions present in cells. Cisplatin and carboplatin, as well as oxaliplatin, are alkylating agents. They impair cell function by forming covalent bonds

with the amino, carboxyl, sulfhydryl, and phosphate groups in biologically important molecules.

Other agents are mechlorethamine, cyclophosphamide, chlorambucil, ifosfamide. They work by chemically modifying a cell's DNA.

Anti-metabolites (L01B)

Anti-metabolites masquerade as purines ((azathioprine, mercaptopurine)) or pyrimidines—which become the building blocks of DNA. They prevent these substances from becoming incorporated in to DNA during the "S" phase (of the cell cycle), stopping normal development and division. They also affect RNA synthesis. Due to their efficiency, these drugs are the most widely used cytostatics.

Plant alkaloids and terpenoids (L01C)

These alkaloids are derived from plants and block cell division by preventing microtubule function. Microtubules are vital for cell division, and, without them, cell division cannot occur. The main examples are vinca alkaloids and taxanes.

Vinca alkaloids (L01CA)

Vinca alkaloids bind to specific sites on tubulin, inhibiting the assembly of tubulin into microtubules (M phase of the cell cycle). They are derived from the Madagascar periwinkle, *Catharanthus roseus* (formerly known as *Vinca rosea*). The vinca alkaloids include:

- Vincristine
- Vinblastine
- Vinorelbine
- Vindesine

Podophyllotoxin (L01CB)

Podophyllotoxin is a plant-derived compound which is said to help with digestion as well as used to produce two other cytostatic drugs, etoposide and teniposide. They prevent the cell from entering the G1 phase (the start of DNA replication) and the replication of DNA (the S phase). The exact mechanism of its action is not yet known.

The substance has been primarily obtained from the American Mayapple (*Podophyllum peltatum*). Recently it has been discovered that a rare Himalayan Mayapple (*Podophyllum hexandrum*) contains it in a much greater quantity, but, as the plant is endangered, its supply is limited. Studies have been conducted to isolate the genes involved in the substance's production, so that it could be obtained recombinantly.

Taxanes (L01CD)

The prototype taxane is the natural product paclitaxel, originally known as Taxol and first derived from the bark of the Pacific Yew tree. Docetaxel is a semi-synthetic analogue of paclitaxel. Taxanes enhance stability of microtubules, preventing the separation of chromosomes during anaphase.

Topoisomerase inhibitors (L01CB and L01XX)

Topoisomerases are essential enzymes that maintain the topology of DNA. Inhibition of type I or type II topoisomerases interferes with both transcription and replication of DNA by upsetting proper DNA supercoiling.

- Some type I topoisomerase inhibitors include *camptothecins*: irinotecan and topotecan.

- Examples of type II inhibitors include amsacrine, etoposide, etoposide phosphate, and teniposide. These are semisynthetic derivatives of epipodophyllotoxins, alkaloids naturally occurring in the root of American Mayapple (*Podophyllum peltatum*).

Antineoplastics (L01D)

These include the immunosuppressant dactinomycin (which is used in kidney transplantations), doxorubicin, epirubicin, bleomycin and others.

Newer and experimental approaches

Hematopoietic stem cell transplant approaches

Stem cell harvesting and autologous or hematopoietic stem cell transplantation has been used to allow for higher doses of chemotherapeutic agents where dosages are primarily limited by hematopoietic damage. Years of research in treating solid tumors, particularly breast cancer, with hematopoeitic stem cell transplants, has yielded little proof of efficacy. Hematological malignancies such as myeloma, lymphoma, and leukemia remain the main indications for stem cell transplants.

Isolated infusion approaches

Isolated limb perfusion (often used in melanoma), or isolated infusion of chemotherapy into the liver or the lung have been used to treat some tumours. The main purpose of these approaches is to deliver a very high dose of chemotherapy to tumor sites without causing overwhelming *systemic* damage. These approaches can help control solitary or limited metastases, but they are by definition *not* systemic, and, therefore, do not treat distributed metastases or micrometastases.

Targeted delivery mechanisms

Specially targeted delivery vehicles aim to increase effective levels of chemotherapy for tumor cells while reducing effective levels for other cells. This should result in an increased tumor kill and/or reduced toxicity.

Specially targeted delivery vehicles have a differentially higher affinity for tumor cells by interacting with tumor-specific or tumour-associated antigens.

In addition to their targeting component, they also carry a payload - whether this is a traditional chemotherapeutic agent, or a radioisotope or an immune stimulating factor. Specially targeted delivery vehicles vary in their stability, selectivity, and choice of target, but, in essence, they all aim to increase the maximum effective dose that can be delivered to the tumor cells. Reduced systemic toxicity means that they can also be used in sicker patients, and that they can carry new chemotherapeutic agents that would have been far too toxic to deliver via traditional systemic approaches.

Light water

Light water or Deuterium-Depleted Water (DDW) is a form of water with lower-than-normal levels of the isotope deuterium. Whereas deuterium-rich heavy water is harmful to many animals, experiments have shown that consumption of light water may be beneficial to humans, particularly those undergoing chemotherapy. A 1999 Romanian study found that water with only 30ppm deuterium produced marked improvement in survival rates of mice bombarded with ionizing radiation. A study of four patients with brain metastases from lung cancer found a three-month regimen of light water "noticeably prolonged" their survival time. A 2010 Hungarian study found significant improvement in the survival times of prostate cancer patients treated with light water.

Nanoparticles

Nanoparticles have emerged as a useful vehicle for poorly soluble agents such as paclitaxel. Protein-bound paclitaxel (e.g., Abraxane) or nab-paclitaxel was approved by the U.S. Food and Drug Administration (FDA) in January 2005 for the treatment of refractory breast cancer. This formulation of paclitaxel uses human albumin as a vehicle and not the Cremophor vehicle used in Taxol. Nanoparticles made of magnetic material can also be used to concentrate agents at tumour sites using an externally applied magnetic field.

Dosage

Dosage of chemotherapy can be difficult: If the dose is too low, it will be ineffective against the tumor, whereas, at excessive doses, the toxicity (side effects, neutropenia) will be intolerable to the patient. This has led to the formation of detailed "dosing schemes" in most hospitals, which give guidance on the correct dose and adjustment in case of

toxicity. In immunotherapy, they are in principle used in smaller dosages than in the treatment of malignant diseases.

In most cases, the dose is adjusted for the patient's body surface area, a measure that correlates with blood volume. The BSA is usually calculated with a mathematical formula or a nomogram, using a patient's weight and height, rather than by direct measurement.

Delivery

Most chemotherapy is delivered intravenously, although a number of agents can be administered orally (e.g., melphalan, busulfan, capecitabine). In some cases, isolated limb perfusion (often used in melanoma), or isolated infusion of chemotherapy into the liver or the lung have been used. The main purpose of these approaches is to deliver a very high dose of chemotherapy to tumour sites without causing overwhelming systemic damage.

Depending on the patient, the cancer, the stage of cancer, the type of chemotherapy, and the dosage, intravenous chemotherapy may be given on either an inpatient or an outpatient basis. For continuous, frequent or prolonged intravenous chemotherapy administration, various systems may be surgically inserted into the vasculature to maintain access. Commonly used systems are the Hickman line, the Port-a-Cath or the PICC line. These have a lower infection risk, are much less prone to phlebitis or extravasation, and abolish the need for repeated insertion of peripheral cannulae.

Harmful and lethal toxicity from chemotherapy limits the dosage of chemotherapy that can be given. Some tumors can be destroyed by sufficiently high doses of chemotherapeutic agents. However, these high doses cannot be given because they would be fatal to the patient.

Adverse effects

Chemotherapeutic techniques have a range of side effects that depend on the type of medications used. The most common medications mainly affect the fast-dividing cells of the body, such as blood cells and the cells lining the mouth, stomach, and intestines. Common side effects include:

- Depression of the immune system, which can result in potentially fatal infections. Although patients are encouraged to wash their hands, avoid sick people, and to take other infection-reducing steps, about 85% of infections are due to naturally occurring microorganisms in the patient's own gut and skin. This may manifest as systemic infections, such as sepsis, or as localized outbreaks, such as shingles. Sometimes, chemotherapy treatments are postponed because the immune system is suppressed to a critically low level.
- Fatigue. The treatment can be physically exhausting for the patient, who might already be very tired from cancer-related fatigue. It may produce mild to severe

anemia. Treatments to mitigate anemia include hormones to boost blood production (erythropoietin), iron supplements, and blood transfusions.
- Tendency to bleed easily. Medications that kill rapidly dividing cells or blood cells are likely to reduce the number of platelets in the blood, which can result in bruises and bleeding. Extremely low platelet counts may be temporarily boosted through platelet transfusions. Sometimes, chemotherapy treatments are postponed to allow platelet counts to recover.
- Gastrointestinal distress. Nausea and vomiting are common side effects of chemotherapeutic medications that kill fast-dividing cells. This can also produce diarrhea or constipation. Malnutrition and dehydration can result when the patient doesn't eat or drink enough, or when the patient vomits frequently, because of gastrointestinal damage. This can result in rapid weight loss, or occasionally in weight gain, if the patient eats too much in an effort to allay nausea or heartburn. Weight gain can also be caused by some steroid medications. These side effects can frequently be reduced or eliminated with antiemetic drugs. Self-care measures, such as eating frequent small meals and drinking clear liquids or ginger tea, are often recommended. This is a temporary effect, and frequently resolves within a week of finishing treatment.
- Hair loss. Some medications that kill rapidly dividing cells cause dramatic hair loss; other medications may cause hair to thin. These are temporary effects: hair usually starts growing back a few weeks after the last treatment, sometimes with a tendency to curl that may be called a "chemo perm".

Damage to specific organs may occur, with resultant symptoms:

- Cardiotoxicity (heart damage)
- Hepatotoxicity (liver damage)
- Nephrotoxicity (kidney damage)
- Ototoxicity (damage to the inner ear), producing vertigo
- Encephalopathy (brain dysfunction)

Immunosuppression and myelosuppression

Virtually all chemotherapeutic regimens can cause depression of the immune system, often by paralysing the bone marrow and leading to a decrease of white blood cells, red blood cells, and platelets. The latter two, when they occur, are improved with blood transfusion. Neutropenia (a decrease of the neutrophil granulocyte count below 0.5 x 10^9/litre) can be improved with synthetic G-CSF (granulocyte-colony stimulating factor, e.g., filgrastim, lenograstim).

In very severe myelosuppression, which occurs in some regimens, almost all the bone marrow stem cells (cells that produce white and red blood cells) are destroyed, meaning *allogenic* or *autologous* bone marrow cell transplants are necessary. (In autologous BMTs, cells are removed from the patient before the treatment, multiplied and then re-injected afterwards; in *allogenic* BMTs the source is a donor.) However, some patients still develop diseases because of this interference with bone marrow.

In Japan the government has approved the use of some medicinal mushrooms like *Trametes versicolor*, to counteract depression of the immune system in patients undergoing chemotherapy. The United States' top-ranked cancer hospital, the MD Anderson, has reported that polysaccharide-K (PSK; an extract from *Trametes versicolor*) is a "promising candidate for chemoprevention due to the multiple effects on the malignant process, limited side effects and safety of daily oral doses for extended periods of time." PSK is already used in pharmaceuticals designed to complement chemotherapy such as MC-S. The MD Anderson has also reported that there are 40 human studies, 55 animal studies, 37 *in vitro* studies, and 11 reviews published concerning *Trametes versicolor* or its extract PSK.

Nausea and vomiting

Chemotherapy-induced nausea and vomiting (CINV) is common with many treatments and some forms of cancer. However, some chemotherapy regimens do not have this side effect, and very effective drugs to stop or noticeably reduce this adverse effect are available.

A class of drugs called 5-HT_3 antagonists are the most effective antiemetics and constitute the single greatest advance in the management of nausea and vomiting in patients with cancer. These drugs block one or more of the nerve signals that cause nausea and vomiting. During the first 24 hours after chemotherapy, the most effective approach appears to be blocking the 5-HT_3 nerve signal. Approved 5-HT_3 inhibitors include dolasetron, granisetron, and ondansetron (Zofran). The newest 5-HT_3 inhibitor, palonosetron, also prevents delayed nausea and vomiting, which occurs during the 2–5 days after treatment. Since some patients have trouble swallowing pills, these drugs are often available by injection, as orally disintegrating tablets, or as transdermal patchs.

The substance P inhibitor aprepitant, which became available in 2005, is also effective in controlling the nausea of cancer chemotherapy.

Some studies and patient groups say that the use of cannabinoids derived from marijuana during chemotherapy greatly reduces the associated nausea and vomiting, and enables the patient to eat. Some synthetic derivatives of the active substance in marijuana (Tetrahydrocannabinol or THC) such as Marinol may be practical for this application. Natural marijuana, known as medical cannabis is also used and recommended by some oncologists, though its use is regulated and not legal everywhere.

Secondary neoplasm

Development of secondary neoplasia after successful chemotherapy and/or radiotherapy treatment can occur. The most common secondary neoplasm is secondary acute myeloid leukemia, which develops primarily after treatment with alkylating agents or topoisomerase inhibitors. Other studies have shown a 13.5 fold increase from the general population in the incidence of secondary neoplasm occurrence after 30 years from treatment.

Infertility

Some types of chemotherapy are gonadotoxic and may cause infertility. Chemotherapies with high risk include procarbazine and other alkylating drugs such as cyclophosphamide, ifosfamide, busulfan, melphalan, chlorambucil and chlormethine. Drugs with medium risk include doxorubicin and platinum analogs such as cisplatin and carboplatin. On the other hand, therapies with low risk of gonadotoxicity include plant derivatives such as vincristine and vinblastine, antibiotics such as bleomycinand dactinomycin and antimetabolites such as methotrexate, mercaptopurine and 5-fluoruracil.

Patients may choose between several methods of fertility preservation prior to chemotherapy, including cryopreservation of semen, ovarian tissue, oocytes or embryos.

Other side effects

In particularly large tumors, such as large lymphomas, some patients develop tumor lysis syndrome from the rapid breakdown of malignant cells. Although prophylaxis is available and is often initiated in patients with large tumors, this is a dangerous side effect that can lead to death if left untreated.

Less common side effects include pain, red skin (erythema), dry skin, damaged fingernails, a dry mouth (xerostomia), water retention, and sexual impotence. Some medications can trigger allergic or pseudoallergic reactions.

Some patients report fatigue or non-specific neurocognitive problems, such as an inability to concentrate; this is sometimes called post-chemotherapy cognitive impairment, referred to as "chemo brain" by patients' groups.

Specific chemotherapeutic agents are associated with organ-specific toxicities, including cardiovascular disease (e.g., doxorubicin), interstitial lung disease (e.g., bleomycin) and occasionally secondary neoplasm (e.g., MOPP therapy for Hodgkin's disease).

In other animals

Chemotherapy is used in veterinary medicine similar to in human medicine.

Chapter 5

Insulin Potentiation Therapy

Insulin potentiation therapy (IPT) is an alternative medicine pharmacologic strategy for the chemotherapy of cancer using insulin and low-dose chemotherapy.

The therapeutic approach is said to take advantage of the endogenous molecular biology of cancer cells, specifically insulin and insulin like growth factor secretion, and the interaction of these biochemicals with their specific receptors. By using insulin in conjunction with chemotherapy drugs, significantly less drug (about 10-15 % of a standard dose) can be targeted more specifically and more effectively to cancer cell populations, thus virtually eliminating dose-related side effects while claiming enhancing antineoplastic effects.

Controversy regarding effectiveness

Some physicians have labeled insulin potentiation therapy a form of quackery and have warned against its use

Claimed explanatory molecular biology

The proponents of IPT give the following explanation of the biology of cancer and its cells in order to understand the mechanisms of IPT, which relies upon insulin, the most integral component of IPT, having three significant actions upon cancer cells described below, as well as also dropping blood sugar levels and thus the energy source for cancer. Low blood glucose (below 60 mg/dl) also stimulates secretion of growth hormone, and growth hormone probably helps to strengthen the immune system.

Differentiation between cancer and normal cells

Insulin biologically differentiates cancer cells from normal cells based on insulin receptor concentration.

Insulin can serve to distinguish and differentiate cancer cells from healthy cells in several way. Produced in the pancreas, one of its many functions is the regulation of blood glucose levels. Chiefly, insulin activates a glucose transport protein within all cells – whether they be cancerous or healthy - which allows glucose, the energy source, to enter, thus lowering the blood glucose level.

Like anything else, cancer needs energy to grow. The growth of cancer is abnormally rapid, its sole purpose being to spread, therefore it has a voracious appetite compared to normal cells. Cancer cells have developed the ability to produce insulin and insulin-like growth factor (IGF) themselves; this way they can autonomously increase their glucose uptake.

Being able to produce its own insulin makes cancer different from normal cells, but there is a second abnormality that insulin highlights. Every cell in the body has insulin receptors on the outer surface of its membrane - from 100-100,000 receptors per cell. But cancer cells have a much higher concentration of receptors. Breast cancer cells - for example - have six times more insulin receptors and ten times more IGF receptors per cell than normal cells. As an added boost, insulin is able to react with its own receptors and is also able to cross-react with and activate the IGF receptors on cancer cells. This means that insulin will affect cancer cells sixteen times as strongly as it effects normal tissues. Something else to take into consideration is that ligand effect is a function of receptor concentration. In a particular tissue, the more receptors there are for a certain ligand – such as insulin – the greater the effect of that ligand on that tissue.

By activating the insulin and IGF receptors on cancer cells through the administration of insulin during an IPT treatment, the biological differences of cancer cells can be highlighted – a vital consideration for the safety of cancer chemotherapy.

Modification of cancer cell metabolism

Not only does insulin provide cancer cells with the means to grow, it has also been proven that IGFs are the most potent mitogen - promoter of cell division - for cancer growth.

Now why would growth be a favorable effect in a treatment, which is trying to kill cancer? The answer lies in the killing mechanism of chemotherapy medications. The standard pharmacologic treatment for cancer involves drugs, which are designed to attack cells that are dividing, cell division being the means by which tissue "grows." Cancer cells are rapidly dividing cells, and are constantly going through cell division. There are several phases to cell division, the one called the S-Phase being when cells replicate DNA. There are some chemotherapy agents that are "S-Phase dependent:" they attack cells that are in the S-phase of cell division, not cells in the resting phase.

Unfortunately hair cells, red and white blood cells and cells found in the digestive tract also fall into this category of rapidly dividing cells - the reason why the side effects related to standard chemotherapy are associated with these areas. In order to get a

tumoral response in conventional chemotherapy, a high dose of drugs have to be used and unfortunately healthy cells are affected as well. The chemotherapy drugs by themselves cannot differentiate between rapidly dividing cancer cells and rapidly dividing healthy cells. By implementing insulin in conjunction with chemotherapy drugs, the cancer cells are highlighted as being different based on receptor concentration and are promoted to grow, which makes it likely that more of them will be in the S-phase cycle. These effects allow for the powerful chemo agents to target the cancer cells more specifically, sparing healthy cells and therefore chemo-related side-effects.

Increase in cell membrane permeability

The third effect that insulin has on cancer cells is to activate enzyme activity in the cell membrane making them more permeable.

Cell membranes are largely made up of triglycerides, which are built of fatty acids. The more saturated that a fatty acid is, the higher the melting point (example: butter [a saturated fat with a higher melting point] is solid at room temperature, whereas olive oil [an unsaturated fat with a lower melting point] is a liquid). The enzyme that insulin activates is called delta-9 desaturase and the action of this enzyme is to de-saturate - to make a saturated fat into an unsaturated fat. Delta-9 desaturase - once it has been activated by insulin - de-saturates the fatty acids that make up the cell membrane of cancer cells. This fatty acid – saturated stearic acid– has a melting point of 65 °C. Stearic acid once it has been de-saturated, becomes mono-unsaturated oleic acid, which has a melting point of 5 °C. At physiologic temperatures (the temperature of the body, about 37.5 °C) tristearin – triglyceride with three stearic acids attached that composes the cancer cell membrane - is going to be more "waxy" than "oily" because of its higher melting point. This makes for a less permeable cell membrane. On the other hand, once the insulin has activated the enzyme delta-9 desaturase, the cell membrane of cancer cells is composed of triolein – the triglyceride with three oleic acids attached – with a melting point of 5 °C. This cell membrane will be more permeable at physiologic temperatures. The chemotherapy drugs are thus able to enter the cancer cells more easily because of the increased cell membrane permeability, providing the required intracellular dose intensity to kill the cancer.

Insulin is used in IPT to enhance anticancer drug cytoxicity and safety, via 1) an effect of biological differentiation based on insulin receptor concentration, 2) an effect of metabolic modification to increase the S-phase fraction in cancer cells, enhancing their susceptibility to cell-cycle phase-specific agents, and 3) a membrane permeability effect to increase the intracellular dose intensity of the drugs. Significantly less drug can thus be targeted more specifically and more effectively to cancer cells, all this occurring with a virtual elimination of the dose-related side effects.

Supportive research

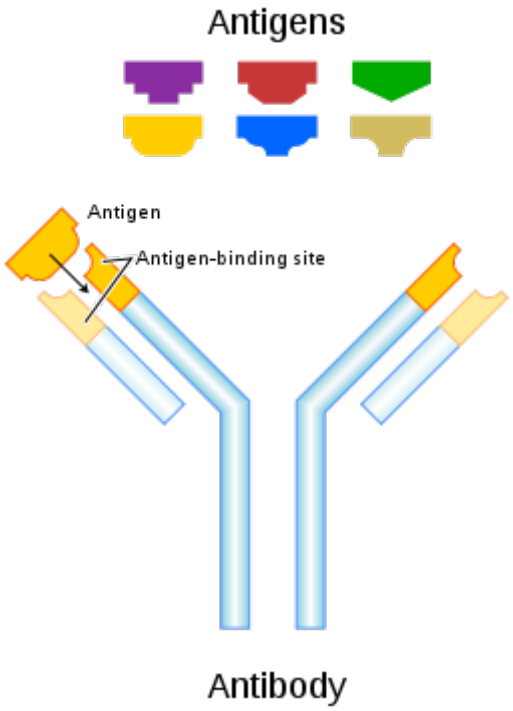
In-vitro studies have shown how IPT works supporting the informal clinical work that has been conducted on hundreds of patients worldwide.

A clinical trial of IPT for treating breast cancer was done in Uruguay and concluded that "The group treated with insulin + methotrexate responded most frequently with stable disease" compared to being treated with methotrexate alone or insulin alone.

In 2000, the National Cancer Institute's Cancer Advisory Panel on Complementary and Alternative Medicine (CAPCAM) invited Drs. Perez Garcia and Ayre to present IPT to them as part of the National Cancer Institute's (NCI's) Best Case Series program.. However CAPCAM have not in the time since undertaken any further research into IPT.

Chapter 6

Monoclonal Antibody Therapy



Each antibody binds only one specific antigen.

Monoclonal antibody therapy is the use of monoclonal antibodies (or mAb) to specifically bind to target cells. This may then stimulate the patient's immune system to attack those cells. It is possible to create a mAb specific to almost any extracellular/ cell surface target, and thus there is a large amount of research and development currently being undergone to create monoclonals for numerous serious diseases (such as rheumatoid arthritis, multiple sclerosis and different types of cancers). There are a number of ways that mAbs can be used for therapy. For example: mAb therapy can be used to destroy malignant tumor cells and prevent tumor growth by blocking specific cell receptors. Variations also exist within this treatment, e.g. radioimmunotherapy, where a

radioactive dose localizes on target cell line, delivering lethal chemical doses to the target.

Structure and function of human and therapeutic antibodies

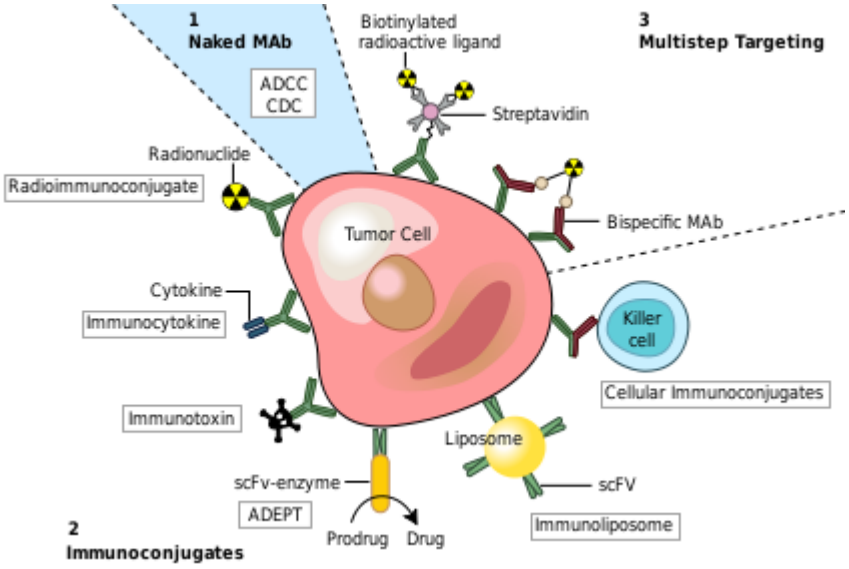
Immunoglobulin G (IgG) antibodies are large heterodimeric molecules, approximately 150 kDa and are composed of two different kinds of polypeptide chain, called the heavy (~50kDa) and the light chain (~25kDa). There are two types of light chains, kappa (κ) and lambda (λ). By cleavage with enzyme papain, the Fab (*fragment-antigen binding*) part can be separated from the Fc (*fragment crystalline*) part of the molecule. The Fab fragments contain the variable domains, which consist of three hypervariable amino acid domains responsible for the antibody specificity embedded into constant regions. There are four known IgG subclasses all of which are involved in Antibody-dependent cellular cytotoxicity.

The immune system responds to the environmental factors it encounters on the basis of discrimination between self and non-self. Tumor cells are not specifically targeted by one's immune system since tumor cells are the patient's own cells. Tumor cells, however are highly abnormal, and many display unusual antigens that are either inappropriate for the cell type, its environment, or are only normally present during the organisms' development (e.g. fetal antigens).

Other tumor cells display cell surface receptors that are rare or absent on the surfaces of healthy cells, and which are responsible for activating cellular signal transduction pathways that cause the unregulated growth and division of the tumor cell. Examples include ErbB2, a constitutively active cell surface receptor that is produced at abnormally high levels on the surface of approximately 30% of breast cancer tumor cells. Such breast cancer is known a HER2 positive breast cancer.

Antibodies are a key component of the adaptive immune response, playing a central role in both in the recognition of foreign antigens and the stimulation of an immune response to them. The advent of monoclonal antibody technology has made it possible to raise antibodies against specific antigens presented on the surfaces of tumors.

Origins of monoclonal antibody therapy



Monoclonal antibodies for cancer. ADEPT, antibody directed enzyme prodrug therapy; ADCC, antibody dependent cell-mediated cytotoxicity; CDC, complement dependent cytotoxicity; MAb, monoclonal antibody; scFv, single-chain Fv fragment.

Immunotherapy developed as a technique with the discovery of the structure of antibodies and the development of hybridoma technology, which provided the first reliable source of monoclonal antibodies. These advances allowed for the specific targeting of tumors both in vitro and in vivo. Initial research on malignant neoplasms found MAb therapy of limited and generally short-lived success with malignancies of the blood. Furthermore treatment had to be specifically tailored to each individual patient, thus proving to be impracticable for the routine clinical setting.

Throughout the progression of monoclonal drug development there have been four major antibody types developed: murine, chimeric, humanised and human.

Initial therapeutic antibodies were simple murine analogues, which contributed to the early lack of success. It has since been shown that these antibodies have: a short half-life in vivo (due to immune complex formation), limited penetration into tumour sites, and that they inadequately recruit host effector functions. To overcome these difficulties the technical issues initially experienced had to be surpassed. Chimeric and humanized antibodies have generally replaced murine antibodies in modern therapeutic antibody applications. Hybridoma technology has been replaced by recombinant DNA technology, transgenic mice and phage display. Understanding of proteomics has proven essential in identifying novel tumour targets.

Murine monoclonal antibodies (suffix *-omab*)

Initially, murine antibodies were obtained by hybridoma technology, for which Kohler and Milstein received a Nobel prize. However the dissimilarity between murine and human immune systems led to the clinical failure of these antibodies, except in some specific circumstances. Major problems associated with murine antibodies included reduced stimulation of cytotoxicity and the formation complexes after repeated administration, which resulted in mild allergic reactions and sometimes anaphylactic shock.

Chimeric and humanized monoclonal antibodies (suffixes *-ximab*, *-zumab* respectively)

To reduce murine antibody immunogenicity, murine molecules were engineered to remove immunogenic content and to increase their immunologic efficiency. This was initially achieved by the production of chimeric and humanized antibodies. Chimeric antibodies are composed of murine variable regions fused onto human constant regions. Human gene sequences, taken from the kappa light chain and the IgG1 heavy chain, results in antibodies that are approximately 65% human. This reduces immunogenicity, and thus increases serum half-life.

Humanised antibodies are produced by grafting murine hypervariable amino acid domains into human antibodies. This results in a molecule of approximately 95% human origin. However it has been shown in several studies that humanised antibodies bind antigen much more weakly than the parent murine monoclonal antibody, with reported decreases in affinity of up to several hundredfold. Increases in antibody-antigen binding strength have been achieved by introducing mutations into the complementarity determining regions (CDR), using techniques such as chain-shuffling, randomization of complementarity determining regions and generation of antibody libraries with mutations within the variable regions by error-prone PCR, E. coli mutator strains, and site-specific mutagenesis.

Human monoclonal antibodies (suffix *-umab*)

Human monoclonal antibodies are produced using transgenic mice or phage display libraries. Human monoclonal antibodies are produced by transferring human immunoglobulin genes into the murine genome, after which the transgenic mouse is vaccinated against the desired antigen, leading to the production of monoclonal antibodies., allowing the transformation of murine antibodies in vitro into fully human antibodies.

Targeted conditions

Cancer

Anti-cancer monoclonal antibodies can be targeted against malignant cells by several mechanisms:

- Radioimmunotherapy (RIT) involves the use of radioactively conjugated murine antibodies against cellular antigens. Most research currently involved their application to lymphomas, as these are highly radio-sensitive malignancies. To limit radiation exposure, murine antibodies were especially chosen, as their high immunogenicity promotes rapid clearance from the body. Tositumomab is an exemplar used for non-Hodgkins lymphoma.

- Antibody-directed enzyme prodrug therapy (ADEPT) involves the application of cancer associated monoclonal antibodies which are linked to a drug-activating enzyme. Subsequent systemic administration of a non-toxic agent results in its conversion to a toxic drug, and resulting in a cytotoxic effect which can be targeted at malignant cells. The clinical success of ADEPT treatments has been limited to date. However it holds great promise, and recent reports suggest that it will have a role in future oncological treatment.

- Immunoliposomes are antibody-conjugated liposomes. Liposomes can carry drugs or therapeutic nucleotides and when conjugated with monoclonal antibodies, may be directed against malignant cells. Although this technique is still in its infancy, significant advances have been made. Immunoliposomes have been successfully used in vivo to achieve targeted delivery of tumour-suppressing genes into tumours, using an antibody fragment against the human transferrin receptor. Tissue-specific gene delivery using immunoliposomes has also been achieved in brain, and breast cancer tissue.

Autoimmune diseases

Monoclonal antibodies used for autoimmune diseases include infliximab and adalimumab, which are effective in rheumatoid arthritis, Crohn's disease and ulcerative Colitis by their ability to bind to and inhibit TNF-α. Basiliximab and daclizumab inhibit IL-2 on activated T cells and thereby help preventing acute rejection of kidney transplants. Omalizumab inhibits human immunoglobulin E (IgE) and is useful in moderate-to-severe allergic asthma.

FDA approved therapeutic antibodies

The first FDA-approved therapeutic monoclonal antibody was a murine IgG2a CD3 specific transplant rejection drug, OKT3 (also called muromonab), in 1986. This drug found use in solid organ transplant recipients who became steroid resistant. Hundreds of

therapies are undergoing clinical trials. Most are concerned with immunological and oncological targets.

Example FDA approved therapeutic monoclonal antibodies

Antibody	Brand name	Approval date	Type	Target	Indication (What it's approved to treat)
Abciximab	ReoPro	1994	chimeric	inhibition of glycoprotein IIb/IIIa	Cardiovascular disease
Adalimumab	Humira	2002	human	inhibition of TNF-α signaling	Several auto-immune disorders
Alemtuzumab	Campath	2001	humanized	CD52	Chronic lymphocytic leukemia
Basiliximab	Simulect	1998	chimeric	IL-2Rα receptor (CD25)	Transplant rejection
Bevacizumab	Avastin	2004	humanized	Vascular endothelial growth factor (VEGF)	Colorectal cancer, Age related macular degeneration
Cetuximab	Erbitux	2004	chimeric	epidermal growth factor receptor	Colorectal cancer, Head and neck cancer
Certolizumab pegol	Cimzia	2008	humanized	inhibition of TNF-α signaling	Crohn's disease

Daclizumab	Zenapax	1997	humanized	IL-2Rα receptor (CD25)	Transplant rejection
Eculizumab	Soliris	2007	humanized	Complement system protein C5	Paroxysmal nocturnal hemoglobinuria
Efalizumab	Raptiva	2002	humanized	CD11a	Psoriasis
Gemtuzumab	Mylotarg	2000	humanized	CD33	Acute myelogenous leukemia (with calicheamicin)
Ibritumomab tiuxetan	Zevalin	2002	murine	CD20	Non-Hodgkin lymphoma (with yttrium-90 or indium-111)
Infliximab	Remicade	1998	chimeric	inhibition of TNF-α signaling	Several autoimmune disorders
Muromonab-CD3	Orthoclone OKT3	1986	murine	T cell CD3 Receptor	Transplant rejection
Natalizumab	Tysabri	2006	humanized	alpha-4 (α4) integrin,	Multiple sclerosis and Crohn's disease
Omalizumab	Xolair	2004	humanized	immunoglobulin E (IgE)	mainly allergy-related asthma
Palivizumab	Synagis	1998	humanized	an epitope of the RSV F protein	Respiratory Syncytial Virus

Panitumumab	Vectibix	2006	human	epidermal growth factor receptor	Colorectal cancer
Ranibizumab	Lucentis	2006	humanized	Vascular endothelial growth factor A (VEGF-A)	Macular degeneration
Rituximab	Rituxan, Mabthera	1997	chimeric	CD20	Non-Hodgkin lymphoma
Tositumomab	Bexxar	2003	murine	CD20	Non-Hodgkin lymphoma
Trastuzumab	Herceptin	1998	humanized	ErbB2	Breast cancer

Therapeutic Monoclonal Antibody Market Future

Since 2000, the therapeutic market for monoclonal antibodies has grown exponentially. The current "big 5" therapeutic antibodies on the market: Avastin, Herceptin (both oncology), Humira, Remicade (both Autoimmune and Infectious Disease 'AIID') and Rituxan (oncology and AIID) accounted for 80% of revenues in 2006.

In the immediate future, it is likely that Genentech/Roche will retain their control over the market (due to ownership of 3 of the "big 5" products), oncology and AIID will remain the mAb segment therapeutic focus (because these are the disease areas addressed by the big 5) and the three most commercially important 'targets' for the mAb class will be VEGF (Avastin), TNF-alpha (Remicade and Humira) and CD20 (Rituxan). Experts forecast that the therapeutic antibody market will continue to be dominated by Oncology and AIID segments (82-84 percent) from 2004 to 2011. Furthermore, experts note a potential for change in the balance between Oncology and AIID in the coming years. While Oncology therapeutics dominated the market in 2004, AIID is expected to dominate by 2011.

Chapter 7

Hydrotherapy

Hubbard Tub with wooden patient lift.

Hydrotherapy, formerly called **hydropathy**, involves the use of water for pain-relief and treating illness. The term hydrotherapy itself is synonymous with the term **water**

cure as it was originally marketed by practitioners and promoters in the 19th century. A hydrotherapist therefore, is someone who practices hydrotherapy.

Water cure has since come to have two opposing definitions, which can cause confusion.

> (a) Water cure therapy – a course of medical treatment by hydrotherapy
> (b) water cure torture – a form of torture in which a person is forced to drink large quantities of water.

The sense used here is the first one, synonymous with the term hydrotherapy, and which precedes recorded use of the second sense.

Hydrotherapy in general encompases a range of approaches and their definitions. These range from approaches and definitions which are either naturally distinct, or made so for marketing purposes, to approaches and definitions which overlap significantly, and which can be difficult to disentangle.

One such overlap pertains to spas. According to the International SPA Association (ISPA), hydrotherapy has long been a staple in European spas. It's the generic term for water therapies using jets, underwater massage and mineral baths (e.g. balneotherapy, Iodine-Grine therapy, Kneipp treatments, Scotch hose, Swiss shower, thalassotherapy) and others. It also can mean a whirlpool bath, hot Roman bath, hot tub, Jacuzzi, cold plunge and mineral bath. These treatments use physical water properties, such as temperature and pressure, for therapeutic purposes, to stimulate blood circulation and treat the symptoms of certain diseases.

Historical background

Various forms of hydrotherapy have been recorded in ancient Egyptian, Greek and Roman civilizations. Egyptian royalty bathed with essential oils and flowers, while Romans had communal public baths for their citizens. Hippocrates prescribed bathing in spring water for sickness. Other cultures noted for a long history of hydrotherapy include China and Japan, this latter being centred primarily around Japanese hot springs, or (onsen). Many such histories predate the Roman thermae.

After an apparent oblivion during the Middle Ages, hydrotherapy was rediscovered during the 18th and 19th centuries by people such as J.S.Hahn, MD, (1696–1773), Vincent Priessnitz (1799–1851), Professor E.F.C. Oertel (1764–1850), and J.H. Rausse (1805–1848).

In the 19th century, a popular revival followed the application of hydrotherapy around 1829, by Priessnitz, a peasant farmer in Gräfenberg, then part of the Austrian Empire. This revival was continued by a Bavarian priest, Sebastian Kneipp (1821–1897), "an able and enthusiastic follower" of Priessnitz, "whose work he took up where Priessnitz left it", after he read a treatise on the cold water cure. In Wörishofen (south Germany), Kneipp developed the systematic and controlled application of hydrotherapy for the support of

medical treatment that was delivered only by doctors at that time. Kneipp's own book *My Water Cure* was published in 1886 with many subsequent editions, and translated into many languages.

A significant factor in the popular revival of hydrotherapy was that it could be practised relatively cheaply at home. The growth of hydrotherapy (or 'hydropathy' to use the name of the time), was thus partly derived from two interacting spheres: "the hydro and the home".

Revival and practice of hydrotherapy

Hydrotherapy as a formal medical tool dates from about 1829 when Vincent Priessnitz (1799–1851), a farmer of Gräfenberg in Silesia, then part of the Austrian Empire, began his public career in the paternal homestead, extended so as to accommodate the increasing numbers attracted by the fame of his cures.

Two English works, however, on the medical uses of water had been translated into German in the century preceding the rise of the movement under Priessnitz. One of these was by Sir John Floyer, a physician of Lichfield, who, struck by the remedial use of certain springs by the neighboring peasantry, investigated the history of cold bathing and published a book the subject in 1702. The book ran through six editions within a few years and the translation was largely drawn upon by Dr J. S. Hahn of Silesia in a work published in 1738.

The other work was a 1797 publication by Dr James Currie of Liverpool on the use of hot and cold water in the treatment of fever and other illness, with a fourth edition published in 1805, not long before his death. It was also translated into German by Michaelis (1801) and Hegewisch (1807). It was highly popular and first placed the subject on a scientific basis. Hahn's writings had meanwhile created much enthusiasm among his countrymen, societies having been everywhere formed to promote the medicinal and dietetic use of water; and in 1804 Professor E.F.C. Oertel of Anspach republished them and quickened the popular movement by unqualified commendation of water drinking as a remedy for all diseases. In him the rising Priessnitz found a zealous advocate, and doubtless an instructor also.

At Gräfenberg, to which the fame of Priessnitz drew people of every rank and many countries, medical men were conspicuous by their numbers, some being attracted by curiosity, others by the desire of knowledge, but the majority by the hope of cure for ailments which had as yet proved incurable. Many records of experiences at Gräfenberg were published, all more or less favorable to the claims of Priessnitz, and some enthusiastic in their estimate of his genius and penetration; Captain R. T. Claridge introduced hydropathy into England in the early 1840s, his writings and lectures, and later those of Sir William James Erasmus Wilson (1809–1884), James Manby Gully and Edward Johnson, making numerous converts, and filling the establishments which opened soon after at Malvern and elsewhere, with Scotland particularly well represented.

From the 1840s, hydropathics were established across Britain. Initially, many of these were small institutions, catering to at most dozens of patients. By the later nineteenth century the typical hydropathic establishment had evolved into a more substantial undertaking, with thousands of patients treated annually for weeks at a time in a large purpose-built building with lavish facilities - baths, recreation rooms and the like - under the supervision of fully trained and qualified medical practitioners and staff.

In Germany, France and America, and in Malvern in England where Wilson and Gully set up their clinics using Malvern water, hydropathic establishments multiplied with great rapidity. Antagonism ran high between the old practice and the new. Unsparing condemnation was heaped by each on the other; and a legal prosecution, leading to a royal commission of inquiry, served but to make Priessnitz and his system stand higher in public estimation.

Increasing popularity soon diminished caution whether the new method would help minor ailments and be of benefit to the more seriously injured. Hydropathists occupied themselves mainly with studying chronic invalids well able to bear a rigorous regimen and the severities of unrestricted crisis. The need of a radical adaptation to the former class was first adequately recognized by John Smedley, a manufacturer of Derbyshire, who, impressed in his own person with the severities as well as the benefits of the cold water cure, practised among his workpeople a milder form of hydropathy, and began about 1852 a new era in its history, founding at Matlock a counterpart of the establishment at Gräfenberg.

Ernst Brand (1826–1897) of Berlin, Raljen and Theodor von Jürgensen of Kiel, and Karl Liebermeister of Basel, between 1860 and 1870, employed the cooling bath in abdominal typhus with striking results, and led to its introduction to England by Dr Wilson Fox. In the Franco-German War the cooling bath was largely employed, in conjunction frequently with quinine; and it was used in the treatment of hyperpyrexia.

The use of heat

Hydrotherapy, especially as promoted during the height of its Victorian revival, has often been associated with the use of cold water, as evidenced by many titles from that era. However, not all therapists limited their practice of hydrotherapy to cold water, even during the height of this popular revival.

The specific use of heat was however often associated with the Turkish bath. This was introduced by David Urquhart into England on his return from the East, and ardently adopted by Richard Barter. The Turkish bath became a public institution, and, with the morning tub and the general practice of water drinking, is the most noteworthy of the many contributions by hydropathy to public health.

Until around 1840, hydropathy was not common in the United States although it was popular in Europe in the 19th century. But in "Nature's Cures", Michael Castleman wrote

that hundreds of 'water-cures' were located on the countryside during the American Civil War.

Hydrotherapy in the United States of America

The first U.S. hydropathic facility has been attributed to Joel Shew (1816–1855), in 1843 or 1844, and to Russell Thatcher Trall ('R.T. Trall'. 1812-1877) in 1844. The *American Cyclopedia* states "the first establishment appears to have been that opened in 1844, at No. 63 Barclay Street, New York", with David Campbell the proprietor and Joel Shew the physician. Campbell also founded the *Water Cure Journal*

Metcalfe attributes the first establishment to Dr Charles Munde, although this is not supported by Munde himself, or by historical evidence now available. Munde describes himself as becoming familiar with Priessnitz' methods around 1836, and later migrating from Germany, where he treated scarlet fever cases in Dresden during the winter of 1845-46. Munde's son recalls that the family went to the area now called Florence, Massachusetts "in the early fifties", after his father had struggled "for nearly a year in New York in search of a practice". A blind African American man named David Ruggles had previously set up a water cure practice, and after his death in 1849, Charles Munde learned "of the opportunity to take up his favorite method", which led him to pick up where Ruggles left off, thence to the naming of Florence, and accordingly, the name of the *Florence Water Cure*, also called the *Munde Water Cure*.

By 1850, it was said that "now there are probably more than one hundred", along with numerous books and periodicals, including the New York *Water Cure Journal*, which had "attained an extent of circulation equalled by few monthlies in the world". By 1855, there were attempts by some to weigh the evidence of treatments in vogue at that time.

The experience of Mary S. Gove and Dr Thomas L. Nichols illustrates this growth. In 1844, Dr. Wesselboeft opened a "water cure house" in Brattleboro, Vermont, which Mary S. Gove attended to observe Wesselhoeft's practice, following which she was resident physician at the Lebanon Springs establishment. She then went to New York, where she observed Dr Shew's establishment in Bond Street, and in May 1845, opened her own establishment at 261 Tenth-Street, where she gave lectures, took board and day patients, and attended out-door practice. "The first two years I had a large number of board-patients, who came from a distance, from Connecticut, Northern New York, Rhode Island, Ohio, Kentucky, and several from the Southern States". A few years later, the character of her practice had changed, involving fewer board patients, as establishments opened throughout the country. Gove teamed up with Dr Nichols after they became acquainted in 1848. Nichols reports that his own attention was first drawn to water cure "by the celebrated letter of Bulwer, which was an earnest and enthusiastic, but in some respects mistaken advocacy of the system".

Other notable American hydropathy proponents of that era were R.T. Trall, who wrote several works and co-edited the *Water Cure Journal*, Following the introduction of hydrotherapy to the U.S., John Harvey Kellogg employed it at Battle Creek Sanitarium,

which opened in 1866, where he strove to improve the scientific foundation for hydrotherapy. Other notable hydropathic centers of the era included the Cleveland Water Cure Establishment, founded in 1848, which operated successfully for two decades, before being sold to an organisation which transformed it into an orphanage.

At its height, there were over 200 water-cure establishments in the United States, most located in the northeast. Few of these lasted into the postbellum years, although some survived into the 20th century including institutions in Scott (Cortland County), Elmira, Clifton Springs and Dansville. While none were located in Jefferson County, the Oswego Water Cure operated in the city of Oswego.

Hydrotherapy and spa tourism

The growth of hydrotherapy, and various forms of hydropathic establishments, resulted in a form of tourism, both in the UK, and especially in Europe. At least one book listed English, Scottish, Irish and European establishments suitable for each specific malady, while another focused primarily on German spas and hydropathic establishments, but including other areas. While many bathing establishments were open all year round, doctors advised patients not to go before May, "nor to remain after October. English visitors rather prefer cold weather, and they often arrive for the baths in May, and return again in September. Americans come during the whole season, but prefer summer. The most fashionable and crowded time is during July and August". In Europe, interest in various forms of hydrotherapy and spa tourism continued unabated through the 19th century and into the 20th century, where "in France, Italy and Germany, several million people spend time each year at a spa." In 1891, when Mark Twain toured Europe and discovered that a bath of spring water at Aix-les-Bains soothed his rheumatism, he described the experience as "so enjoyable that if I hadn't had a disease I would have borrowed one just to have a pretext for going on".

This was not the first time such forms of spa tourism had been popular in Europe and the U.K. Indeed,

in Europe, the application of water in the treatment of fevers and other maladies had, since the seventeenth century, been consistently promoted by a number of medical writers. In the eighteenth century, taking to the waters became a fashionable pastime for the wealthy classes who decamped to resorts around Britain and Europe to cure the ills of over-consumption. In the main, treatment in the heyday of the British spa consisted of sense and sociability: promenading, bathing, and the repetitive quaffing of foul-tasting mineral waters.

Hydrotherapeutic mechanisms and modern medicine

Modern medicine's successes, particularly with drug therapy, removed or replaced many water-related therapies during the mid-20th century. Nowadays, water therapy may be restricted to use in physical therapy, and as a cleansing agent. However, it is also used as

a medium for delivery of heat and cold to the body, which has long been the basis for its application.

Hydrotherapy involves a range of methods and techniques, many of which use water as a medium to facilitate thermoregulatory reactions for therapeutic benefit. While the physiological mechanisms were initially poorly understood, the therapeutic benefits have long been recognised, even if the reason for the therapeutic benefit was in dispute. For example, in November 1881, the *British Medical Journal* noted that hydropathy was a specific instance, or "particular case", of general principles of thermodynamics. That is, "the application of heat and cold in general", as it applies to physiology, mediated by hydropathy. In 1883, another writer stated "Not, be it observed, that hydropathy is a water treatment after all, but that water is the medium for the application of heat and cold to the body". Thus, the "active agents in the treatment (are) heat and cold", of which water is little more than the vehicle, and not the only one".

With improved knowledge of physiological mechanisms, practitioners wrote specifically of the use of hot and cold applications to produce "profound reflex effects", including vasodilation and vasoconstriction. These cause changes in blood flow and associated metabolic functions, via physiological mechanisms, including those of thermoregulation, that are these days fairly well understood, and which underpin the contemporary use of hydrotherapy. Although standard anatomy and physiology textbooks make only passing reference, if any, to hydrotherapy, some of the best descriptions of the underlying physiology upon which hydrotherapy relies, are to be found in such textbooks. For example, one of the best succinct descriptions of blood redistribution (which is fundamental to the above-mentioned reflex reaction), quoted below, is from a standard textbook.

...by constricting or dilating arterioles in specific areas of the body, such as skeletal muscles, the skin, and the abdominal region, it is possible not only to regulate the blood pressure but also to alter the distribution of blood in various parts of the body.

Examples of hydrotherapy applications

Before World War II, various forms of hydrotherapy were used to treat alcoholism, and it is used today in alternative medicine. For instance, the basic text of the Alcoholics Anonymous fellowship, *Alcoholics Anonymous*, reports that A.A. co-founder Bill Wilson was treated by hydrotherapy for his alcoholism in the early 1930s.

The use of water to treat rheumatic diseases has a long history. It continues to be used as an adjunct to therapy, including in nursing, where its use is now long established. It continues to be widely used for burn treatment, although shower-based hydrotherapy techniques have been increasingly used in preference to full-immersion methods, partly for the ease of cleaning the equipment and reducing infections due to contamination.

Hydrotherapeutic modalities

The appliances and arrangements by means of which heat and cold are brought to bear are (a) packings, hot and cold, general and local, sweating and cooling; (b) hot air and steam baths; (c) general baths, of hot water and cold; (d) sitz (sitting), spinal, head and foot baths; (e) bandages (or compresses), wet and dry; also (f) fomentations and poultices, hot and cold, sinapisms, stupes, rubbings and water potations, hot and cold.

Submersive hydrotherapy

Hydrotherapy which involves submerging all or part of the body in water can involve several types of equipment:

- Full body immersion tanks (a "Hubbard tank" is a large size)
- Arm, hip, and leg whirlpool

Whirling water movement, provided by mechanical pumps, has been used in water tanks since at least the 1940s. Similar technologies have been marketed for recreational use under the terms "hot tub" or "spa".

Hydropathic establishment

A **hydropathic establishment** is a place where people receive hydropathic treatment. They are commonly built in spa towns, where mineral-rich or hot water occurs naturally.

Several hydropathic institutions wholly transferred their operations away from therapeutic purposes to become tourist hotels in the late 20th century whilst retaining the name 'Hydro'. There are several prominent examples in Scotland at Crieff, Peebles and Seamill amongst others.

Examples of hydropathic establishments

Note: For European and U.K. establishments, where there is no citation alongside an establishment, it is safe to assume that reference to it was found in one of the citations placed atop the list for efficiency. Additional citations are added where there is also another source of interest.

Europe

List as at 1840 by Claridge, with additional citations. Geographical names per that era.

Austria, Silesia

- *Graefenberg* (Priessnitz's establishment), Graefenberg, Silesia (c.1829~?).
- Dr Joseph Weiss' hydro, Freiwaldau, Silesia (1831~1841).
- Karlsbrunn (between Freiwaldau, Jagerndorf & Feidenthal). Dr Malik
- Weidenau, on the slopes of the Sudates. Dr Frolich.
- Schroth's establishment, Lindeweise, Silesia.

Archduchy of Austria

- Dr Wilhelm Winternitz's establishment, Kaltenleutgeben, Austria (June 1865-?).
- Laale, near Kaltenleutgeben. Dr. Granichstadten, author of Hydriasiologia.
- Dr Johan Emmel's *Priesnitz Establishment*, Kaltenleutgeben,

United Kingdom

England

- *Stand Steadbury*, Hertfordshire (founded by Weiss) (1841-?).
- *Grafenberg House*, Malvern, (founder Dr James Wilson) (June 1842-c1867 - death of Wilson).
- *Tudor House*, Malvern founder Dr James Manby Gully (October 1842-c1872 - retirement of Gully).
- Sudbrook Park, Richmond, Surrey (founder, Weiss) (1844-?).
- *Ben Rhydding Hydro*, Ilkley near Leeds. (1844–1939)
- *Metcalfe's London Hydro* (1898–1919).
- *Smedley's Hydro*, Matlock, Derbyshire (1860s-1950s)
- *West of England Hydro*, Limpley Stoke (1862~1899).

Scotland, 19th century

- *Angusfield*, Aberdeen (1850 -)
- *Athole*, Pithlocry (1880 -)
- *Bridge of Allan* (1855~1886+)
- *Callander* (1882 -)
- *Cluny Hill*, at Forres (1864~1874+)
- *Crieff*, at Crieff (1868-current)

United States of America

- First known establishment at No. 63 Barclay St., New York. (1844-?). Proprietor David Campbell Physician Joel Shew.
- New Lebanon Springs Water-Cure, Albany (2nd Dr Shew establishment), (May 1845-).
- Brattleborough Hydropathic Establishment, aka Dr. Robert Wesselhoeft's water cure house (c.1844-1871). 3rd in U.S.A.
- David Ruggles' water cure house, Florence, Massachusetts (c.1844-1849).
- Oyster Bay water cure, Long Island (3rd Dr Shew estab.), (1847-).
- Dr. E.E. Denniston's *Round Hill Water-Cure*, Northhampton, Massachusetts (1847-1860+).
- Cleveland Water Cure Establishment, Cleveland, Ohio (1848–1868).
- Dr Munde's *Florence Water Cure* (c.1850 - ?).
- Oswego Water Cure, Oswego, New York

Wienerwald, Austria (1835-?).

Bohemia

- Elisenbad, Near Chrudin. Dr. Weidenhoffer.
- Dobrawitz, near Jungbunzlau. Dr. Schmidt.
- Leitmeritz. Dr. Lauda.

Kuechelbad, near Prague. Dr. Kanzler. **Moravia**

- Czenrahora, around Olmutz.
- Sulowitz, near Brunn.
- Hoznau, near Prerau
- Budischan, near Iglau
- Gross Ullersdorf, near Olmutz. Dr. Gross

Hungary and Transylvania

- Peterwardein (director unknown to Claridge)
- Oedenburg (director unknown to Claridge)
- Hermanstadt (director unknown to Claridge)
- Muhlan, near Inspruck, in the Tyrol. Dr. Fritz

Prussia

- Oberrigk, near

- *Craiglockhart Hydropathic*, Edinburgh (1880~1915)
- *Deeside*, near Cults [1874 (Heathcote) and 1899 (Murtle)]
- *Dunblane (Philps?)*, at Dunblane (1870~1936?)
- *Gilmour Hill*, Glasgow (c.1857 -)
- *Glenburn*, Rothesay, Bute (1843 -)
- *Kilmacolm* (1880–1882)
- *Kim Pier*, Dunoon (1846-)
- *Kyles of Bute*, Port Bannantyne, Bute (1877 -)
- *Lochhead*: Aberdeen (1851~1868).
- *Peebles*, at Peebles (1881-current)
- *Pitlochry*, at Pithlochry (1879 -)
- *Seamill*, near West Kilbride (1880 -)
- *Shandon*, near Helensburgh (~1877~1919).
- *Skelmorlie*, Wemyss Bay (1880~1984)
- *St Helens* and *Waverly*: Melrose (1869)

Scotland, 1920s

- *Ard-Gairney Private Hydropathic*, Kinross
- *Atholl Hotel Hydro*, St. Andrews
- *Garrison Hydro*, Millport
- *Grampian Hills Hydro*, Crieff.
- *Taymouth Castle*

(c.1850s).

- Dr. Henry Foster's Clifton Springs Sanitarium (c.mid-to-late 19th century).
- Battle Creek Sanitarium (1866-World War II).
- Pennoyer's *Kenosha Water Cure*, Wisconsin (C.1870-1890).
- *Pennoyer Sanitarium* (followed on from Kenosha Water Cure after fire: 1890-?).

Trebnitz & Breslau. Dr. Lehman
- Alt Scheitnig, near Breslau. Dr. Burkner.
- Berlin. Directed by Major Plehwe, partner Dr. Beck.
- Marienbad.
- Bendler Strosse, No. 8, Berlin. Dr. Moser. Plus 3rd Berlin establishment
- Koethen, near Berlin. Mr Falkenstein, author of *The wonderful cures of Graefenberg*.
- Gorhrishowo, near Bromberg, in Grand Duchy of Posen. Dr. Barschewitz.
- Kunzendorf, near Neurode, in province of Glatz. Mr Niederfuhr.
- Marienberg, near Boppart around Coblentz. Dr. Schmitz, editor of the *Journal on Hydropathy*.

Bavaria

- Alexandersbad Hydropathic Establishment, near Wuniedel. Dr. Fickentscher/Fikenher. (pre-1840-1860s+).
- Streitberg, between Erlangen and Baireuth
- Schafflarn, near Munich. Dr. Horner
- Munich,

Hydro, Taymouth

Ireland

- *Dr Curtin's Hydropathic Establishment*, Glenbrook, County Cork (1858~1870s).
- *St Ann's Hydropathic Establishment*, Blarney, Co.Cork. (Founder Dr Richard Barter

India

- *Dr Kannan Pugazhendi, Sparrc Institute Chennai India*

Wales

- Llandudno Hydropathic Establishment (c.1872~1905).

- **Unclear**
  - The Rick James Institute.

Nymphenburg Strasse, No.86
- Lake Starnberg. Dr. Schnitzlein, also author of a work on Hydropathy.
- Schallersdorf, near Erlangen. Professor Dr. Fleischmann.
- Dr. Oertel, Anspach.

Württemberg

- Dr. Bentsch, near Ulm.

Saxony

- Dr. Muller, in Swiss Saxony, near Pirna in Bila valley.
- Kreischa, near Dresden. Dr. Stecher.
- Muldenthal, near Frieberg. Mr. Munde, author of a hydropathic work.

Saxe Gotha

- Elgersburg. Dr. Piutti, appointed by Duke of Saxe Coburg Gotha in 1838

Saxe Weimar

- Ilmenau hydropathic establishment (Drs Schwabe, Fitzler, Baumbach, Preller) (c.1841-1865+). (Claridge says "Dr Sitzler")

Brunswick

- Kaulnitz. Director not named.

Poland

- Warsaw. Dr. Sauvan

Russia

- St. Petersburg. Dr. Harnish.

Belgium

- Ghent. Practitioner unknown.
- Another near Brussels. Practitioner unknown.

France

- Dr. Bigel, Strasburg.
- Dr. Baldau, Paris.
- Dr Beni-Barden's establishment, Auteuil, near Paris.
- Dr Fleury's hydropathic establishment, Bellevne, France (c.1860-?).

Others

- Tiefenau hydropathic establishment (Dr. Winkler) (c.1860s-?).
- Dr J.H. Rausse's establishment, Mecklenburg, Germany (c.1837-?).

Chapter 8

Electroconvulsive Therapy

Electroconvulsive therapy (**ECT**), also known as **electroshock**, is psychiatric treatment in which seizures are electrically induced in anesthetized patients for therapeutic effect. Today, ECT is most often used as a treatment for severe depression which has not responded to other treatment, and is also used in the treatment of mania (often in bipolar disorder), and catatonia. It was first introduced in the 1930s and gained widespread use as a form of treatment in the 1940s and 1950s; today, an estimated 1 million people worldwide receive ECT every year, usually in a course of 6–12 treatments administered two or three times a week.

Electroconvulsive therapy can differ in its application in three ways: electrode placement, frequency of treatments, and the electrical waveform of the stimulus. These three forms of application have significant differences in both adverse side effects and positive outcomes. After treatment, drug therapy is usually continued, and some patients receive continuation/maintenance ECT. In the United Kingdom and Ireland, drug therapy is continued during ECT.

Informed consent is a standard of modern electroconvulsive therapy. Involuntary treatment is uncommon in the United States and is typically only used in cases of great extremity, and only when all other treatment options have been exhausted and the use of ECT is believed to be a potentially life saving treatment. Similarly, national audits of ECT use in Scotland and Ireland have demonstrated that the vast majority of patients treated give informed consent. Although it was a source of significant controversies in the past and got frowned upon, recent years have seen an increased acceptance of ECT as a safe, effective and economical tool for the treatment of some mental illnesses. However, it is rarely used as the first line of treatment.

Guidelines for treatment

Experts disagree on whether ECT is an appropriate first-line treatment or if it should be reserved for patients who have not responded to other interventions such as medication and psychotherapy.

The American Psychiatric Association (APA) 2001 guidelines give the primary indications for ECT among patients with depression as a lack of response to, or intolerance of, antidepressant medications; a good response to previous ECT; and the need for a rapid and definitive response (e.g. because of psychosis or a risk of suicide). The decision to use ECT depends on several factors, including the severity and chronicity of the depression, the likelihood that alternative treatments would be effective, the patient's preference and capacity to consent, and a weighing of the risks and benefits.

Some guidelines recommend cognitive behavioral therapy or other psychotherapy before ECT is used. However, treatment resistance is widely defined as lack of therapeutic response to two antidepressants at adequate doses for an adequate duration and with good compliance. The APA states that at times patients will prefer to receive ECT over alternative treatments, but commonly the opposite will be the case.

The APA ECT guidelines state that severe major depression with psychotic features, manic delirium, or catatonia are conditions where there is a clear consensus favoring early ECT. The UK's National Institute for Health and Clinical Excellence (NICE) guidelines recommend ECT for patients with severe depression, catatonia, or prolonged or severe mania. Indeed, the updated (2009) NICE guidelines for depression also provide for the use of maintenance ECT (where ECT is given at longer intervals to prevent relapse), although the guidance stresses the need for further study. The 2001 APA guidelines also support the use of ECT for relapse prevention.

The 2001 APA ECT guidelines say that ECT is rarely used as a first-line treatment for schizophrenia but is considered after unsuccessful treatment with antipsychotic medication, and may also be considered in the treatment of patients with schizoaffective or schizophreniform disorder. The 2003 NICE ECT guidelines do not recommend ECT for schizophrenia, and this has been supported by meta-analytic evidence showing no or little benefit versus placebo, or in combination with antipsychotic drugs, including Clozapine.

The NICE 2003 guidelines state that doctors should be particularly cautious when considering ECT treatment for women who are pregnant and for older or younger people, because they may be at higher risk of complications with ECT. The 2001 APA ECT guidelines say that ECT may be safer than alternative treatments in the infirm elderly and during pregnancy, and the 2000 APA depression guidelines stated that the literature supports the safety for mother and fetus, as well as the efficacy during pregnancy.

Non-clinical patient characteristics

About 70 percent of ECT patients are women. This is almost entirely due to women being at twice the risk of depression. Older and more affluent patients are also more likely to receive ECT. The use of ECT treatment is "markedly reduced for ethnic minorities."

Efficacy

ECT Manages or remisses psychological problems temporarily; but it is not a cure

Researchers are still divided regarding the validity of ECT, and the publications that argue for its efficacy do so only for short terms of one to six months.

ECT on its own does not usually have a sustained benefit. Half those who remit then relapse within six months. This is similar to the rate of relapse after discontinuing antidepressant medication, and is a function of the usual severity and chronicity of pre-existing illness rather than ECT itself. The relapse rate in the first six months is reduced by the use of psychatric medications or further ECT, but remains high.

In a 2010 review of placebo controlled studies Bentall and Read found ECT to give slightly higher recovery/remission rates to sham-ECT during treatment but equal rates after on follow up after treatment[161]. Sham ECT is the placebo control where the patient doesn't get an electric shock.

Their conclusions are as follows:

"Given the strong evidence of persistent and, for some, permanent brain dysfunction, primarily evidenced in the form of retrograde and anterograde amnesia, and the evidence of a slight but significant increased risk of death, the cost-benefit analysis for ECT is so poor that its use cannot be scientifically justified."

Probability of remission

The 1999 U.S. Surgeon General's Report on Mental Health summarized psychiatric opinion at the time about the effectiveness of ECT. It stated that both clinical experience and published studies had determined ECT to be effective (with an average 60 to 70 percent remission rate) in the treatment of severe depression, some acute psychotic states, and mania. Its effectiveness had not been demonstrated in dysthymia, substance abuse, anxiety, or personality disorder. The report stated that ECT does not have a long-term protective effect against suicide and should be regarded as a short-term treatment for an acute episode of illness, to be followed by continuation therapy in the form of drug treatment or further ECT at weekly to monthly intervals.

A 2004 large multicentre clinical follow-up study of ECT patients in New York—describing itself as the first systematic documentation of the effectiveness of ECT in community practice in the 65 years of its use—found remission rates of only 30 to 47 percent, with 64 percent of those relapsing within six months. However, when patients with co-morbid personality disorders or who were suffering from schizoaffective disorder were removed from the analysis, the remission rates climbed to 60-70%.

Degree of effectiveness

All systematic published reviews of the literature have concluded that ECT is effective in the treatment of depression. In 2003, The UK ECT Review group published a systematic review and meta-analysis comparing ECT to placebo and antidepressant drugs. This meta-analysis demonstrated a large effect size for ECT versus placebo, and versus antidepressant drugs. In 2006, research psychiatrist Colin A. Ross reviewed the placebo-controlled trials one-by-one and found that no single study showed a significant difference between real and placebo ECT at one month post-treatment. Dr. Ross was highly critical of other published reviews, which concluded that ECT is effective, and Ross stated that these reviews often relied primarily on studies that were not placebo-controlled. However, Dr. Ross's analysis does not include a statistical synthesis in contrast to the well conducted meta-analytic evidence presented by the UK ECT review group in 2003.

Adverse effects

Aside from effects in the brain, the general physical risks of ECT are similar to those of brief general anesthesia; the United States' Surgeon General's report says that there are "no absolute health contraindications" to its use. Immediately following treatment the most common adverse effects are confusion and memory loss. The state of confusion usually disappears after a few hours. It can be tolerated by pregnant women who are not suffering major complications. It can be used with diabetic or obese patients, and with caution in those whose cancers are in remission or under control. It can be used in some immunocompromised patients. It must be used very cautiously in people with epilepsy or other neurological disorders because by its nature it provokes small tonic-clonic seizures, and so would likely not be given to a person whose epilepsy is not well-controlled. Some patients experience muscle soreness after ECT. This is due to the muscle relaxants given during the procedure and rarely due to muscle activity. The death rate due to ECT is around 4 per 100,000 procedures.

Effects on memory

It is the purported effects of ECT on long-term memory that give rise to much of the concern surrounding its use. The acute effects of ECT can include amnesia, both retrograde (for events occurring before the treatment) and anterograde (for events occurring after the treatment). However, the vast majority of these effects are short lived. Memory loss and confusion are more pronounced with bilateral electrode placement rather than unilateral, and with outdated sine-wave rather than brief-pulse currents. The vast majority of modern treatment uses brief pulse currents. Research by Harold Sackeim has shown that excessive current causes more risk for memory loss, and using right-sided electrode placement may reduce verbal memory disturbance.

Retrograde amnesia is most marked for events occurring in the weeks or months before treatment, with one study showing that although some people lose memories from years prior to treatment, recovery of such memories was "virtually complete" by seven months

post-treatment, with the only enduring loss being memories in the weeks and months prior to the treatment. Anterograde memory loss is usually limited to the time of treatment itself or shortly afterwards. In the weeks and months following ECT these memory problems gradually improve, but some people have persistent losses, especially with bilateral ECT. One published review summarizing the results of questionnaires about subjective memory loss found that between 29% and 55% of respondents believed they experienced long-lasting or permanent memory changes. In 2000, American psychiatrist Sarah Lisanby and colleagues found that bilateral ECT left patients with more persistently impaired memory of public events as compared to RUL ECT.

Some studies have found that patients are often unaware of cognitive deficits induced by ECT. For example, in June 2008, a Duke University study was published assessing the neuropsychological effects and attitudes in patients after ECT. Forty-six patients participated in the study, which involved neuropsychological and psychological testing before and after ECT. The study documented substantial cognitive impairment after ECT on a variety of memory tests, including "verbal memory for word lists and prose passages and visual memory of geometric designs." The study further found that a significant number of patients believed that their memory had improved after ECT despite the fact that neuropsychological testing clearly showed the opposite. As stated by the researchers, "Indeed, there was a slight trend towards [patients reporting] improved memory functioning, despite the objective neuropsychological data indicating significantly lower recognition and delayed recall." Based on their findings, the authors issued the following recommendation:

"When ECT is provided to adolescents, the potential impact of such cognitive changes should be discussed with the patients and their parents or guardians in terms of implications for not only the patient's emotional functioning but cognitive functioning as well, particularly upon his or her academic performance. In summary, we argue that an individual cost-benefit analysis should be made in light of the implications of the potential benefits versus costs of ECT upon improving emotional functioning and the impact that potential memory changes may have on real-world functioning and quality of life."

Severe memory loss from ECT is described in an autobiographical book, *Doctors of Deception: What They Don't Want You to Know about Shock Treatment*.

Controversy over long-term effects on general cognition

According to prominent ECT researcher Harold Sackeim, "despite over fifty years of clinical use and ongoing controversy", until 2007 there had "never been a large-scale, prospective study of the cognitive effects of ECT." In this first-ever large-scale study (347 subjects), Sackeim and colleagues found that at least some forms (namely bilateral application and outdated sine-wave currents) of ECT "routine[ly]" lead to "adverse cognitive effects," including global cognitive deficits and memory loss, that persist for up to six months after treatment, suggesting that the induced deficits may be permanent. The authors also warned that their findings did not suggest that right-unilateral ECT did not

also lead to chronic cognitive deficits. However, the several limitations of this study include the lack of a depressed control group with which to compare memory decay over 6 months. The measure of autobiographical memory used, the Columbia Autobiographical Short-Form (AMI-SF) is not capable of showing memory improvement, with scores at followup expressed as percentages of baseline.

Harold Sackeim can be seen in a videotaped deposition briefly discussing the findings of this study and why, in his opinion, earlier studies had failed to find evidence of long-term harm from ECT. Despite over fifty years of clinical use, Sackeim states that prior to 2001, "the field itself never really had an opportunity to have a discussion about patients who have complaints about long-term memory loss." In this video clip, Sackeim also reveals that at a California ECT conference with 200 practitioners present, when polled as to whether they think ECT can lead to chronic cognitive deficits, two-thirds raised their hands. Sackeim says this was "almost a watershed moment for the field", and was the "first time *publicly* that the field itself said 'no' to the position that it can't happen."

In July 2007, a second study was published concluding that ECT routinely leads to chronic, substantial cognitive deficits, and the findings were not limited to any particular forms of ECT. The study, led by psychiatrist Glenda MacQueen and colleagues, found that patients treated with ECT for bipolar disorder show marked deficits across multiple cognitive domains. According to the researchers, "Subjects who had received remote ECT had further impairment on a variety of learning and memory tests when compared with patients with no past ECT. This degree of impairment could not be accounted for by illness state at the time of assessment or by differential past illness burden between patient groups." Despite the findings of chronic, global cognitive deficits in post-ECT patients, MacQueen and colleagues suggest that it is "unlikely that such findings, even if confirmed, would significantly change the risk–benefit ratio of this notably effective treatment."

Six months after the publication of the Sackeim study documenting routine, long-term memory loss after ECT, prominent ECT researcher Max Fink published a review in the journal *Psychosomatics* concluding that patient complaints of memory loss after ECT are "rare" and should be "characterized as somatoform disorders, rather than as evidence of brain damage, thus warranting psychological treatment for such disorders." Based on his findings, Fink suggests that, "Instead of endorsing these reports as the direct consequence of ECT, especially in patients who have recovered from their depressive illness, lost their suicidal drive, and have improved social functioning, is it not more useful to accept the complaint as a somatoform disorder, explore the basis in the individual's history and experience, and offer appropriate supportive treatment?"

Most recent reviews of the literature and other articles continue to characterize ECT as safe and effective. For example, in June 2009, Portuguese researchers published a review on the safety and efficacy of ECT in an article entitled, *Electroconvulsive Therapy: Myths and Evidences.* In their review, the researchers conclude that ECT is an "efficient, safe and even life saving treatment for several psychiatric disorders." In 2008, Yale researchers published a review on the safety and efficacy of ECT in elderly patients.

According to the authors, "ECT is well established as a safe and effective treatment for several psychiatric disorders." And in a June 2009 article published in the *Journal of ECT*, Iranian researchers observe that, "Despite the wide consensus over the safety and efficacy of electroconvulsive therapy (ECT), it still faces negative publicity and unfavorable attitudes of patients and families."

Psychiatrist Peter Breggin, chief editor of the journal *Ethical Human Psychology and Psychiatry*, is a leading critic of ECT who believes the procedure is neither safe nor effective. In a published article reviewing the findings of Harold Sackeim's 2007 study on the cognitive effects of ECT, Breggin accuses Max Fink and other pro-ECT researchers of having a history of "systematically covering up damage done to millions of [ECT] patients throughout the world." He disagrees with the position that findings of chronic, global cognitive deficits should have no bearing on the risk-benefit ratio of ECT, and he believes it's important to address the "actual impact of these losses on the lives of individual patients." In a section of his paper entitled *Destroying Lives*, Dr. Breggin writes, "Even when these injured people can continue to function on a superficial social basis, they nonetheless suffer devastation of their identities due to the obliteration of key aspects of their personal lives. The loss of the ability to retain and learn new material is not only humiliating and depressing but also disabling. Even when relatively subtle, these activities can disrupt routine activities of living."

A study published in 2004 in the *Journal of Mental Health* reported that 35 to 42% of patients responding to a questionnaire reported ECT resulted in loss of intelligence. The study also reported, "There is no overlap between clinical and consumer studies on the question of benefit."

Doctors of Deception: What They Don't Want You to Know About Shock Treatment reports before-and-after IQ testing of persons receiving ECT, including the author, that show 30 to 40 point losses.

A recent opinion article by a neuropsychologist and a psychiatrist in Dublin suggests that ECT patients who experience cognitive problems following ECT should be offered some form of cognitive rehabilitation. The authors say that the failure to attempt to rehabilitate patients may be partly responsible for the negative public image of ECT. The article speculates on what aspects of such rehabilitation might be useful, without reviewing the literature on its presence or absence.

Effects on brain structure

Considerable controversy exists over the effects of ECT on brain tissue although a number of mental health associations, including the American Psychiatric Association, have concluded that there is no evidence that ECT causes structural brain damage. A 1999 report by the United States Surgeon General states, "The fears that ECT causes gross structural brain pathology have not been supported by decades of methodologically sound research in both humans and animals". However, the word "gross" is a synonym for major, leaving the possibility open for real brain damage which the US Surgeon

General considers minor. However, not all experts agree that ECT does not cause brain damage, and two studies have been published since 2007 finding that at least some forms of ECT may result in *widespread, persisting, generalized cognitive dysfunction*, which might support claims that ECT causes brain damage.

A leading critic of ECT, psychiatrist Peter Breggin has published books and journalistic reviews of the literature purporting to show that ECT routinely causes brain damage as evidenced by a considerable list of studies in humans and animals. In particular, Dr. Breggin asserts that animal and human autopsy studies have shown that ECT routinely causes '*widespread pinpoint hemorrhages and scattered cell death*.' According to Dr. Breggin, the 1990 APA task force report on ECT ignored much of the scientific literature pointing out the negative effects of electroshock therapy. For example, in 1952 Hans Hartelius conducted and published an animal study on cats entitled *Cerebral Changes Following Electrically Induced Convulsions* in which a double-blind microscopic pathology examination showed that it was possible to distinguish the 8 shocked animals from the 8 non-shocked animals with remarkable accuracy based on statistically significant structural changes to the brain, including vessel wall changes, gliosis, and nerve cell changes. Based on the detection of shadow cells and neuronophagia, Hartelius determined that there was irreversible damage to neurons associated with electroshock.

Proponents argue that the addition of hyperoxygenation and refinement in technique in the last thirty years has made ECT safe, and a majority of published reviews in recent decades have reflected this position. In a 2004 study designed to evaluate whether modern ECT techniques lead to identifiable brain damage, twelve monkeys underwent daily electroshock for six weeks under conditions meant to simulate human ECT; the animals were then sacrificed and their brains were compared to monkeys undergoing anesthesia alone. According to the researchers, "None of the ECT-treated monkeys showed pathological findings."

There are recent animal studies that have documented significant brain damage after an electroshock series. For example, in 2005, Russian researchers published a study entitled, *Electroconvulsive Shock Induces Neuron Death in the Mouse Hippocampus: Correlation of Neurodegeneration with Convulsive Activity*. In this study, the researchers found that after an electroshock series, there was a significant loss of neurons in parts of the brain and particularly in defined parts of the hippocampus where up to 10% of neurons were killed. The researchers conclude that "the main cause of neuron death is convulsions evoked by electric shocks." In 2008, Portuguese researchers conducted a rat study aimed at answering the question of whether an electroshock series causes structural changes in vulnerable parts of the brain. According to the authors, "This study answers positively the question of whether repeated administration of ECS seizures can cause brain lesions. Our data are consistent with findings from other animal models and from human studies in showing that neurons located in the entorhinal cortex and in the hilus of the dentate gyrus are particularly vulnerable to repeated seizures." However, they question the applicability of their own research with respect to Electroconvulsive therapy in humans: "An important caveat of our results is that it is unclear to what extent they are relevant to the use of electroconvulsive therapy in psychiatry, because the protocol employed in this

study is different from that used clinically. Evidence from previous studies (Gombos et al., [1999]; Vaidya et al., [1999]) and from our pilot experiments indicates that treating rats either with five to ten widely spaced ECS (at 24- or 48-hr schedules) or with two stimulations only 2 hr apart does not lead to loss of hippocampal neurons".

Many expert proponents of ECT maintain that the procedure is safe and does not cause brain damage. Dr. Charles Kellner, a prominent ECT researcher and former chief editor of the *Journal of ECT* states in a recent published interview that, "There are a number of well-designed studies that show ECT does not cause brain damage and numerous reports of patients who have received a large number of treatments over their lifetime and have suffered no significant problems due to ECT." Dr. Kellner cites specifically to a study purporting to show an absence of cognitive impairment in eight subjects after more than 100 lifetime ECT treatments. One of the authors of the cited study, Harold Sackeim, published a large-scale study less than a month after this interview concluding that the type of ECT used in the eight patients receiving the 100 lifetime treatments, bilateral sine wave, routinely leads to persistent, global cognitive deficits (discussed supra). Dr. Kellner states that, "Rather than cause brain damage, there is evidence that ECT may reverse some of the damaging effects of serious psychiatric illness."

Effects in pregnancy

If steps are taken to decrease potential risks, ECT is generally accepted to be relatively safe during all trimesters of pregnancy, particularly when compared to pharmacological treatments. Suggested preparation for ECT during pregnancy includes a pelvic examination, discontinuation of nonessential anticholinergic medication, uterine tocodynamometry, intravenous hydration, and administration of a nonparticulate antacid. During ECT, elevation of the pregnant woman's right hip, external fetal cardiac monitoring, intubation, and avoidance of excessive hyperventilation are recommended. Much of the medical literature in this area is composed of case studies of single or twin pregnancies, and although some have reported serious complications, the majority have found ECT to be safe. ECT is not performed on the fetus.

Administration

Informed consent is sought before treatment. Patients are informed about the risks and benefits of the procedure. Patients are also made aware of risks and benefits of other treatments and of not having the procedure done at all. Depending on the jurisdiction the need for further inputs from other medical professionals or legal professionals may be required. ECT is usually given on an in-patient basis. Prior to treatment a patient is given a short-acting anesthetic such as methohexital, etomidate, or thiopental, a muscle relaxant such as suxamethonium (succinylcholine), and occasionally atropine to inhibit salivation.

Both electrodes can be placed one on the same side of the patient's head. This is known as unilateral ECT. Unilateral ECT is used first to minimize side effects (memory loss). When electrodes are placed on both sides of the head, this is known as bilateral ECT. In bifrontal ECT, an uncommon variation, the electrode position is somewhere between

bilateral and unilateral. Unilateral is thought to cause fewer cognitive effects than bilateral but is considered less effective. In the USA most patients receive bilateral ECT. In the UK almost all patients receive bilateral ECT.

The electrodes deliver an electrical stimulus. The stimulus levels recommended for ECT are in excess of an individual's seizure threshold: about one and a half times seizure threshold for bilateral ECT and up to 12 times for unilateral ECT. Below these levels treatment may not be effective in spite of a seizure, while doses massively above threshold level, especially with bilateral ECT, expose patients to the risk of more severe cognitive impairment without additional therapeutic gains. Seizure threshold is determined by trial and error ("dose titration"). Some psychiatrists use dose titration, some still use "fixed dose" (that is, all patients are given the same dose) and others compromise by roughly estimating a patient's threshold according to age and sex. Older men tend to have higher thresholds than younger women, but it is not a hard and fast rule, and other factors, for example drugs, affect seizure threshold.

ECT machines

Most modern ECT machines deliver a brief-pulse current, which is thought to cause fewer cognitive effects than the sine-wave currents which were originally used in ECT. A small minority of psychiatrists in the USA still use sine-wave stimuli. Sine-wave is no longer used in the UK or Ireland. Typically, the electrical stimulus used in ECT is about 800 milliamps and has up to several hundred watts, and the current flows for between one and 6 seconds. In the USA, ECT machines are manufactured by two companies, Somatics, which is owned by psychiatrists Richard Abrams and Conrad Swartz, and Mecta. The Food and Drug Administration has classified the devices used to administer ECT as Class III medical devices. Class III is the highest-risk class of medical devices. In the UK, the market for ECT machines was long monopolized by Ectron Ltd, although in recent years some hospitals have started using American machines. Ectron Ltd was set up by psychiatrist Robert Russell, who together with a colleague from the Three Counties Asylum, Bedfordshire, invented the Page–Russell technique of intensive ECT.

Variations in international practice

There is wide variation in ECT use between different countries, different hospitals, and different psychiatrists. International practice varies considerably from widespread use of the therapy in many western countries to a small minority of countries that do not use ECT at all, such as Slovenia. Guidelines on the use of ECT are stringent in the USA and the UK. Modern standards are not always followed throughout the world and not all countries that use ECT have written technical standards. The use of both anesthesia and muscle relaxants is universally recommended in the administration of ECT. If anesthesia and muscle relaxants are not used the procedure is called unmodified ECT. In a minority of countries such as Japan, India, and Nigeria, ECT may be used without anesthesia. WHO has called for a worldwide ban on unmodified ECT and the topic is currently being debated in countries like India. The practice has been recently abolished in Turkey's largest psychiatric hospital. A major difficulty for developing countries in eliminating

unmodified ECT is a lack of trained anesthesiologists available to administer the procedure. A small minority of countries never seek consent before administering ECT. This significantly uneven application of ECT around the world continues to make ECT a controversial procedure.

Sarah Hall reports, "ECT has been dogged by conflict between psychiatrists who swear by it, and some patients and families of patients who say that their lives have been ruined by it. It is controversial in some European countries such as the Netherlands and Italy, where its use is severely restricted".

United States

In the United States, a survey of psychiatric practice in the late 1980s found that an estimated 100,000 people received ECT annually, with wide variation between metropolitan statistical areas. Accurate statistics about the frequency, context and circumstances of ECT in the United States are difficult to obtain because only a few states have reporting laws that require the treating facility to supply state authorities with this information. One state which does report such data is Texas, where in the mid-1990s ECT was used in about one third of psychiatric facilities and given to about 1,650 people annually. Usage of ECT has since declined slightly; in 2000–01 ECT was given to about 1,500 people aged from 16 to 97 (in Texas it is illegal to give ECT to anyone under sixteen). ECT is more commonly used in private psychiatric hospitals than in public hospitals, and minority patients are underrepresented in the ECT statistics. In the United States, ECT is usually given three times a week; in the UK, it is usually given twice a week. Occasionally it is given on a daily basis. A course usually consists of 6–12 treatments, but may be more or fewer. Following a course of ECT some patients may be given continuation or maintenance ECT with further treatments at weekly, fortnightly or monthly intervals. A few psychiatrists in the USA use multiple-monitored ECT (MMECT) where patients receive more than one treatment per anesthetic. Electroconvulsive therapy is not a required subject in US medical schools and not a required skill in psychiatric residency training. Privileging for ECT practice at institutions is a local option, no national certification standards are established, and no ECT-specific continuing training experiences are required of ECT practitioners.

United Kingdom

In the United Kingdom in 1980, an estimated 50,000 people received ECT annually, with use declining steadily since then to about 12,000 per annum. It is still used in nearly all psychiatric hospitals, with a survey of ECT use from 2002 finding that 71 percent of patients were women and 46 percent were over 65 years of age. Eighty-one percent had a diagnosis of mood disorder; schizophrenia was the next most common diagnosis. Sixteen percent were treated without their consent. In 2003, the National Institute for Clinical Excellence, a government body which was set up to standardize treatment throughout the National Health Service in England and Wales, issued guidance on the use of ECT. Its use was recommended "only to achieve rapid and short-term improvement of severe symptoms after an adequate trial of treatment options has proven ineffective and/or when

the condition is considered to be potentially life-threatening in individuals with severe depressive illness, catatonia or a prolonged manic episode". The guidance received a mixed reception. It was welcomed by an editorial in the British Medical Journal but the Royal College of Psychiatrists launched an unsuccessful appeal. The NICE guidance, as the British Medical Journal editorial points out, is only a policy statement and psychiatrists may deviate from it if they see fit. Adherence to standards has not been universal in the past. A survey of ECT use in 1980 found that more than half of ECT clinics failed to meet minimum standards set by the Royal College of Psychiatrists, with a later survey in 1998 finding that minimum standards were largely adhered to, but that two-thirds of clinics still fell short of current guidelines, particularly in the training and supervision of junior doctors involved in the procedure. A voluntary accreditation scheme, ECTAS, was set up in 2004 by the Royal College, but as of 2006 only a minority of ECT clinics in England, Wales, Northern Ireland and the Republic of Ireland have signed up.

Mechanism of action

The aim of ECT is to induce a therapeutic clonic seizure (a seizure where the person loses consciousness and has convulsions) lasting for at least 15 seconds. Although a large amount of research has been carried out, the exact mechanism of action of ECT remains elusive. The main reasons for this are that the human brain can not be studied directly before and after ECT and therefore scientists rely on animal models of depression and ECT, with major limitations. While animal models are acknowledged to model merely aspects of depressive illness, human and animal brains are very similar at a molecular level, enabling detailed study of the molecular mechanisms involved in ECT

There is a vast literature on the effects of Electroconvulsive Shock (ECS) in animals. In animal models of depression, particularly "Learned helplessness" and "Social defeat", there is evidence of pruning of normally dense synaptic connections in the hippocampus, a richly connected area deep in the temporal lobe which is vital in controlling both mood and memory. ECS has been shown to increase levels of Brain-derived neurotrophic factor (BDNF) and Vascular Endothelial Growth Factor (VEGF) in the rodent hippocampus. This reverses the toxic effects of depression on this area of the brain, increasing both new synapse formation and the formation of new brain cells (hippocampal neurogenesis). Both these effects have been noted to be present in antidepressant-treated animals, however they are neither necessary nor sufficient for antidepressant response. ECT is a more robust inducer of these neuroplastic effects than antidepressants.Electroconvulsive Therapy (ECT) has also been shown to increase serum brain-derived neurotrophic factor (BDNF) in drug resistant depressed patients. This suggests a common molecular mechanism of action, albeit in need of much further study.

Legal status

Informed consent

It is widely acknowledged internationally that obtaining the written, informed consent of the patient is important before ECT is administered. The World Health Organization, in its 2005 publication "Human Rights and Legislation WHO Resource Book on Mental Health," specifically states, "ECT should be administered only after obtaining informed consent."

In the US, this doctrine places a legal obligation on a doctor to make a patient aware of: the reason for treatment, the risks and benefits of a proposed treatment, the risks and benefits of alternative treatment, and the risks and benefits of receiving no treatment. The patient is then given the opportunity to accept or reject the treatment. The form states how many treatments are recommended and also makes the patient aware that the treatment may be revoked at anytime during a course of ECT. The Surgeon General's Report on Mental Health states that patients should be warned that the benefits of ECT are short-lived without active continuation treatment in the form of drugs or further ECT, and that there may be some risk of permanent, severe memory loss after ECT. The report advises psychiatrists to involve patients in discussion, possibly with the aid of leaflets or videos, both before and during a course of ECT.

To demonstrate what he believes should be required to fully satisfy the legal obligation for informed consent, one psychiatrist, working for an anti-psychiatry organisation, has formulated his own consent form using the consent form developed and enacted by the Texas Legislature as a model.

In the UK, in order for consent to be valid it requires an explanation in "broad terms" of the nature of the procedure and its likely effects. One review from 2005 found that only about half of patients felt they were given sufficient information about ECT and its adverse effects and another survey found that about fifty percent of psychiatrists and nurses agreed with them.

A 2005 study published in the *British Journal of Psychiatry* described patients' perspectives on the adequacy of informed consent before ECT. The study found that, "About half (45–55%) of patients reported they were given an adequate explanation of ECT, implying a similar percentage felt they were not." The authors also stated:

"Approximately a third did not feel they had freely consented to ECT even when they had signed a consent form. The proportion who feel they did not freely choose the treatment has actually increased over time. The same themes arise whether the patient had received treatment a year ago or 30 years ago. Neither current nor proposed safeguards for patients are sufficient to ensure informed consent with respect to ECT, at least in England and Wales."

Involuntary ECT

Procedures for involuntary ECT vary from country to country depending on local mental health laws. Legal proceedings are required in some countries, while in others ECT is seen as another form of treatment that may be given involuntarily as long as legal conditions are observed. Involuntary electroshock contravenes the principle of autonomy in medical ethics. The maxim of autonomy is "Voluntas aegroti suprema lex." This rule states that the will of the patient is supreme. It implies that a patient has the right to consent to, or to refuse a medical treatment, such as ECT. Persons considered not to be of sound mind are in many jurisdictions considered incapable of giving true consent. In such a case, the patient's "assent" may be sought; opinions are divided as to whether this should be routinely done, or whether a patient who is not competent to consent to therapy should retain the right to refuse it.

Citizens in western societies often undergo emergency medical procedures when they have lost the capacity to consent (such as neurosurgery after head injury). Under these circumstances, the principles of benificence and non-maleficence must be adhered to.

United States

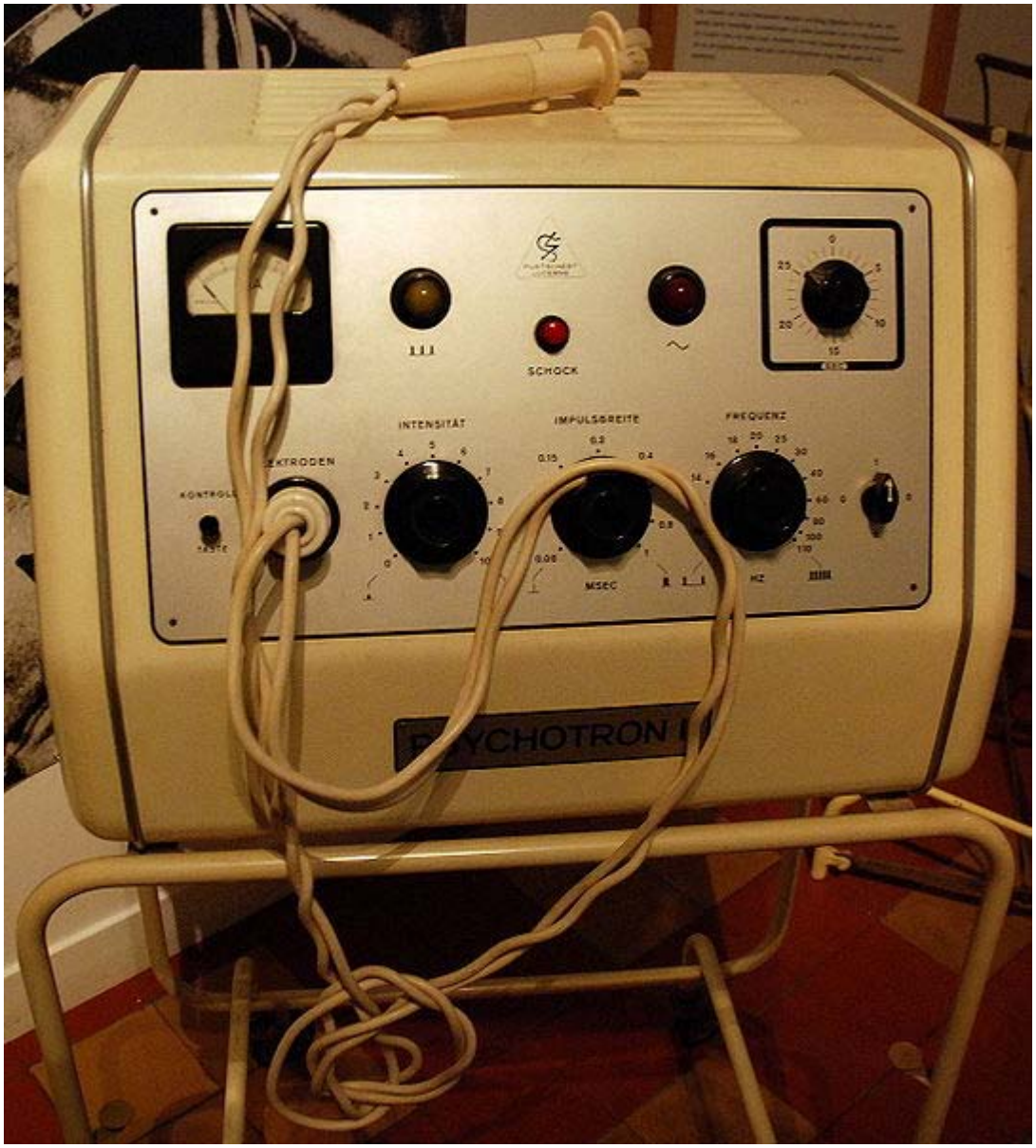
In most states in the USA, a judicial order following a formal hearing is needed before a patient can be forced to undergo involuntary ECT. Patients may be represented by legal counsel at the hearing. Oregon Revised Statutes allow for involuntary ECT with the signature of a physician independent of the patient's facility, and no judicial order or legal counsel are required. According to the Surgeon General's Report on Mental Health, "As a rule, the law requires that such petitions are granted only where the prompt institution of ECT is regarded as potentially lifesaving, as in the case of a person in grave danger because of lack of food or fluid intake caused by catatonia." However, there are legal loopholes that thwart strict adherence to this principle. For example, an American citizen was being forced to undergo ECT against his will in 2009, even though his life was not in danger. In this March 17, 2009 video, the man, his mother, and advocates, speak out against his forced ECT. The description of the video states that "Though Sandford, 54, is not charged with any crime, he has received over 40 such rounds of shocks on an outpatient basis so far – even after his original mental problems have long since subsided and he has repeatedly asked for the shocks to stop. Over the objections of Sandford, his mother and friends, his legal conservator at Lutheran Social Service of MN (LSSMN) has gone to court and succeeded in mandating a continuation of the procedure." Twin Cities Indymedia asserts "Like all other USA states, Minnesota has [legal] loopholes allowing [its] citizens to receive electroshock over their expressed wishes."

Great Britain

Until 2009 in England and Wales, the Mental Health Act 1983 allowed the use of ECT on detained patients whether or not they had capacity to consent to it, so long as the treatment was likely to alleviate or prevent deterioration in a condition and was authorized by a psychiatrist from the Mental Health Act Commission's panel. However,

following amendments which took effect in 2009, ECT may not be given to a patient who has capacity to refuse to consent to it, irrespective of his or her detention under the Act, although treatment may still be given to capacious patients in an emergency under Section 62 of the Act. If the treating psychiatrist thinks the need for treatment is urgent they may start a course of ECT before authorization. About 2,000 people a year in England and Wales are treated without their consent under the Mental Health Act. In Scotland the Mental Health (Care and Treatment) (Scotland) Act 2003 also gives patients with capacity the right to refuse ECT.

History



A psychotron, apparatus for administering elektroshocks

As early as the 16th century, agents to produce seizures were used to treat psychiatric conditions. In 1785, the therapeutic use of seizure induction was documented in the London Medical Journal. Convulsive therapy was introduced in 1934 by Hungarian neuropsychiatrist Ladislas J. Meduna who, believing mistakenly that schizophrenia and epilepsy were antagonistic disorders, induced seizures with first camphor and then metrazol (cardiazol). Within three years metrazol convulsive therapy was being used worldwide. In 1937, the first international meeting on convulsive therapy was held in Switzerland by the Swiss psychiatrist Muller. The proceedings were published in the American Journal of Psychiatry and, within three years, cardiazol convulsive therapy was being used worldwide. Italian Professor of neuropsychiatry Ugo Cerletti, who had been using electric shocks to produce seizures in animal experiments, and his colleague Lucio Bini developed the idea of using electricity as a substitute for metrazol in convulsive therapy and, in 1937, experimented for the first time on a person. Sherwin B. Nuland, having discussed the matter with a first-hand observer in the 1970s, gave the following description of the results of the first use of ECT on a person:

"They thought, 'Well, we'll try 55 volts, two-tenths of a second. That's not going to do anything terrible to him.' So they did that. [...] This fellow — remember, he wasn't even put to sleep — after this major grand mal convulsion, sat right up, looked at these three fellows and said, 'What the fuck are you assholes trying to do?' Well, they were happy as could be, because he hadn't said a rational word in the weeks of observation."

ECT soon replaced metrazol therapy all over the world because it was cheaper, less frightening and more convenient. Cerletti and Bini were nominated for a Nobel Prize but did not receive one. By 1940, the procedure was introduced to both England and the US. In Germany and Austria it was promoted by Friedrich Meggendorfer. Through the 1940s and 1950s the use of ECT became widespread. ECT is the only form of shock treatment still performed by modern medicine.

In the early 1940s, in an attempt to reduce the memory disturbance and confusion associated with treatment, two modifications were introduced: the use of unilateral electrode placement and the replacement of sinusoidal current with brief pulse. It took many years for brief-pulse equipment to be widely adopted Unilateral ECT has never been popular with psychiatrists and is still only given to a minority of ECT patients. In the 1940s and early 1950s ECT was usually given in "unmodified" form, without muscle relaxants, and the seizure resulted in a full-scale convulsion. A rare but serious complication of unmodified ECT was fracture or dislocation of the long bones. In the 1940s psychiatrists began to experiment with curare, the muscle-paralysing South American poison, in order to modify the convulsions. The introduction of suxamethonium (succinylcholine), a safer synthetic alternative to curare, in 1951 led to the more widespread use of "modified" ECT. A short-acting anesthetic was usually given in addition to the muscle relaxant in order to spare patients the terrifying feeling of suffocation that can be experienced with muscle relaxants.

The steady growth of antidepressant use along with negative depictions of ECT in the mass media led to a marked decline in the use of ECT during the 1950s to the 1970s. The

Surgeon General stated there were problems with electroshock therapy in the initial years before anesthesia was routinely given and, *these now antiquated practices contributed to the negative portrayal of ECT in the popular media.* The New York Times described the public's negative perception of ECT as being caused mainly by one movie, "For Big Nurse in *One Flew Over the Cuckoo's Nest,* it was a tool of terror, and in the public mind *shock therapy* has retained the tarnished image given it by Ken Kesey's novel: dangerous, inhumane and overused".

In 1976, Dr. Blatchley demonstrated the effectiveness of his constant current, brief pulse device ECT. This device eventually largely replaced earlier devices because of the reduction in cognitive side effects, although some ECT clinics in the US still use sine-wave devices. The 1970s saw the publication of the first American Psychiatric Association task force report on electroconvulsive therapy (to be followed by further reports in 1990 and 2001). The report endorsed the use of ECT in the treatment of depression. The decade also saw criticism of ECT. Specifically critics pointed to shortcomings such as noted side effects, the procedure being used as a form of abuse, and uneven application of ECT. The use of ECT declined until the 1980s, "when use began to increase amid growing awareness of its benefits and cost-effectiveness for treating severe depression". In 1985 the National Institute of Mental Health and National Institutes of Health convened a consensus development conference on ECT and concluded that, whilst ECT was the most controversial treatment in psychiatry and had significant side-effects, it had been shown to be effective for a narrow range of severe psychiatric disorders.

Due to the backlash noted previously, national institutions reviewed past practices and set new standards. In 1978, The American Psychiatric Association released its first task force report in which new standards for consent were introduced and the use of unilateral electrode placement was recommended. The 1985 NIMH Consensus Conference confirmed the therapeutic role of ECT in certain circumstances. The American Psychiatric Association released its second task force report in 1990 where specific details on the delivery, education, and training of ECT were documented. Finally in 2001 the American Psychiatric Association released its latest task force report. This report emphasizes the importance of informed consent, and the expanded role that the procedure has in modern medicine.

Patient experience

The APA ECT taskforce guidelines report findings that most patients find ECT no worse than going to the dentist, and many found it less stressful than the dentist. They report that other research finds that most patients would voluntarily receive ECT again if needed.

NICE ECT guidelines report that some individuals consider ECT to have been a beneficial and lifesaving treatment, while others reported feelings of terror, shame and distress, and found it positively harmful and an abusive invasion of personal autonomy, especially when administered without their consent.

Individual positive depictions

Kitty Dukakis, wife of politician Michael Dukakis, reports in a *Newsweek* article mostly positive effects from electroconvulsive therapy, and regards memory loss as an acceptable price to pay for relief from depression.

For me, the memory issues are real but manageable. Things I lose generally come back. Other memories I prefer to lose, including those about the depression I was suffering. But there are some memories—of meetings I have attended, people's homes I have visited—that I don't want to lose but I can't help it. They generally involve things I did two weeks before and two weeks after ECT. Often they are just wiped out....I have learned ways to partly compensate for whatever loss I still experience. I call my sister Jinny, Michael and my kids, asking what my niece Betsy's phone number is, what we did yesterday and what we are planning to do tomorrow. I apologize prior to asking. I wonder when they are going to run out of patience with "Kitty being Kitty." I hate losing memories, which means losing control over my past and my mind, but the control ECT gives me over my disabling depression is worth this relatively minor cost. It just is.

American psychotherapist Martha Manning's autobiographical *Undercurrents* acknowledges the downside of treatment: "I felt like I'd been hit by a truck for a while, but that was, comparatively speaking, not so bad," as well as the upside: "Afterwards, I thought, do regular people feel this way all the time? It's like you've not been in on a great joke for the whole of your life."

In his autobiographical book *Electroboy*, American writer Andy Behrman describes undergoing ECT as a treatment for bipolar disorder while under house-arrest: "I wake up thirty minutes later and think I am in a hotel in Acapulco. My head feels as if I have just downed a frozen margarita too quickly. My jaws and limbs ache. But I am elated."

Curtis Hartmann, a lawyer in western Massachusetts, stated: "ECT, a treatment of last resort for severe, debilitating depression, is all that has ever worked for me. I awaken about 20 minutes later, and although I am still groggy with anesthesia, much of the hellish depression is gone. It is a disease that for me, literally steals me from myself—a disease that executes me and then forces me to stand and look down at my corpse. Thankfully, ECT has kept my monster at bay, my hope intact".

Beverley Callard is a British actress, best known for her role as Liz McDonald in Coronation Street. In her recently published autobiography titled "Unbroken", she describes her experience with ECT for severe depression, stating that the treatment was responsible, in part for her recovery.

Individual negative depictions

Depictions of severe long-term, permanent memory loss

Ernest Hemingway, American author, committed suicide shortly after ECT at the Mayo Clinic in 1961. He is reported to have said to his biographer, "Well, what is the sense of ruining my head and erasing my memory, which is my capital, and putting me out of business? It was a brilliant cure but we lost the patient...."

In a letter to the editor published in the *Washington Post* in December, 2000, registered nurse Barbara C. Cody wrote that her life was forever changed by 13 outpatient ECTs she received in 1983. She wrote,

"Shock 'therapy' totally and permanently disabled me. EEGs [electroencephalograms] verify the extensive damage shock did to my brain. Fifteen to 20 years of my life were simply erased; only small bits and pieces have returned. I was also left with short-term memory impairment and serious cognitive deficits. ... Shock 'therapy' took my past, my college education, my musical abilities, even the knowledge that my children were, in fact, my children. I call ECT a rape of the soul."

Similarly, writer Johnanton Cott claims to have completely lost 15 years of memory in *On the Sea of Memory: A Journey from Forgetting to Remembering.*

Despite former patients having reported devastating, permanent amnesia and cognitive impairment since ECT was first invented, the first lawsuit for ECT amnesia, Marilyn Rice v. John Nardini, was not brought until 1975; dozens of suits followed. While there have been a few settlements, including one for half a million dollars, no former patient had won a case until 2005. In a 2005 South Carolina court proceeding, Peggy S. Salters became the first ECT survivor to win a jury verdict and compensation. Ms. Salters sued Palmetto Baptist Medical Center in Columbia, as well as the three doctors responsible for her care, for an intensive course of outpatient ECT that she received in 2000, at age 55 years old, that caused her to lose all memories of the past 30 years of her life, including all memories of her husband of three decades, then deceased, and the births of her three children. She held a Masters of Science in nursing and, prior to the ECT, had a long career as a psychiatric nurse; but, as a result of the ECT, lost her knowledge of nursing skills and was unable to return to work. The jury awarded Salters $635,177 in compensation for her inability to work. The judgement was upheld upon appeal in an unpublished opinion.

Accounts of severe cognitive diminishment

Liz Spikol, the senior contributing editor of *Philadelphia Weekly*, wrote of her ECT in 1996,

"Not only was the ECT ineffective, it was incredibly damaging to my cognitive functioning and memory. But sometimes it's hard to be sure of yourself when everyone

'credible' — scientists, ECT docs, researchers — are telling you that your reality isn't real. How many times have I been told my memory loss wasn't due to ECT but to depression? How many times have I been told that, like a lot of other consumers, I must be perceiving this incorrectly? How many times have people told me that my feelings of trauma related to the ECT are misplaced and unusual? It's as if I was raped and people kept telling me not to be upset—that it wasn't that bad."

Involuntary or other problems in administrating ECT

In 2007, a judge canceled a two-year-old court order that allowed the involuntary electroshock of Simone D., a psychiatric patient at Creedmoor Psychiatric Center in the state of New York. Although Simone spoke only Spanish, she rarely received access to staff fluent in her language. Simone previously had 200 electroshocks. However, she communicated that she did not want more electroshock. Simone stated, "Electroshock causes more pain. I suffer more from shock treatment! "

In 2008, David Tarloff, a psychiatric patient who had received electroshock, assaulted two therapists in the city of New York. Tarloff injured one therapist and killed the other. One of the therapists was Kent Shinbach, a psychiatrist who had an interest in electroconvulsive therapy. "It is not clear whether Dr. Shinbach played any role in Mr. Tarloff's shock therapy". However, Tarloff told investigators that Shinbach had given Tarloff psychiatric treatment at a psychiatric facility initially in 1991.

Bad but vague descriptions

In an interview with *Houston Chronicle* in 1996, Melissa Holliday, a former extra on *Baywatch* and model for *Playboy* stated the ECT she received in 1995, "ruined her life." She went on to state, "I've been through a rape, and electroshock therapy is worse. If you haven't gone through it, I can't explain it."

Chapter 9

Oxygen Therapy

Oxygen piping and regulator, for oxygen therapy, mounted on the wall of an ambulance

Oxygen Regulator for portable D-Cylinder, usually carried in an ambulance's resuscitation kit.

Oxygen therapy is the administration of oxygen as a medical intervention, which can be for a variety of purposes in both chronic and acute patient care. Oxygen is essential for cell metabolism, and in turn, tissue oxygenation is essential for all normal physiological functions.

Room air only contains 21% oxygen, and increasing the fraction of oxygen in the breathing gas increases the amount of oxygen in the blood. It is often only required to raise the fraction of oxygen delivered to 30–35% and this is done by use of a nasal cannula. When 100% oxygen is needed, it may be delivered via a tight-fitting face mask, or by supplying 100% oxygen to an incubator in the case of infants. Oxygen can be administered in other ways, including specific treatments at raised air pressure, such as hyperbaric oxygen therapy.

High blood and tissue levels of oxygen can be helpful or damaging, depending on circumstances and oxygen therapy should be used to benefit the patient by increasing the supply of oxygen to the lungs and thereby increasing the availability of oxygen to the body tissues, especially when the patient is suffering from hypoxia and/or hypoxaemia.

Indications for use

Oxygen is used as a medical treatment in both chronic and acute cases, and can be used in hospital, pre-hospital or entirely out of hospital, dependant on the needs of the patient and the views of the medical professional advising.

Use in chronic conditions

A common use of supplementary oxygen is in patients with chronic obstructive pulmonary disease (COPD), a common long term effect of smoking, who may require additional oxygen to breathe either during a temporary worsening of their condition, or throughout the day and night. It is indicated in COPD patients with $PaO_2 \leq 55mmHg$ or $SaO_2 \leq 88\%$ and has been shown to increase lifespan.

Use in acute conditions

Oxygen is widely used in emergency medicine, both in hospital and by emergency medical services or advanced first aiders.

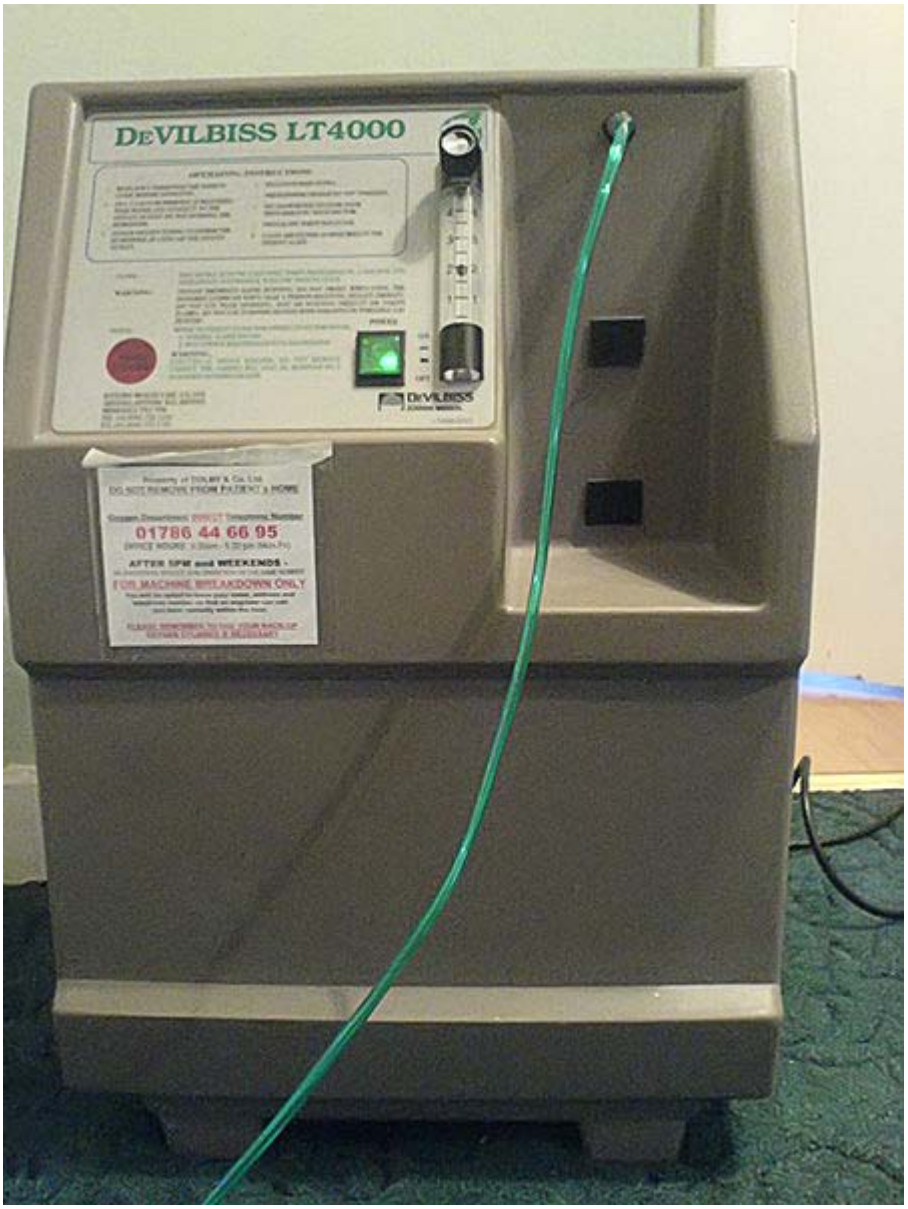
In the pre-hospital environment, high flow oxygen is definitively indicated for use in resuscitation, major trauma, anaphylaxis, major haemorrhage, shock, active convulsions and hypothermia.

It may also be indicated for any other patient where their injury or illness has caused hypoxaemia, although in this case oxygen flow should be moderated to achieve target oxygen saturation levels, based on pulse oximetry (with a target level of 94-98% in most patients, or 88-92% in COPD patients).

For personal use, high concentration oxygen is used as home therapy to abort cluster headache attacks, due to its vaso-constrictive effects.

Storage and sources

Gas cylinders containing oxygen to be used at home. When in use a pipe is attached to the cylinder's regulator and then to a mask that fits over the patient's nose and mouth.



A home oxygen concentrator *in situ* in an emphysema patient's house. The model shown is the DeVILBISS LT 4000.

Oxygen can be separated by a number of methods, including chemical reaction and fractional distillation, and then either used immediately or stored for future use. The main types sources for oxygen therapy are:

1. Liquid storage - Liquid oxygen is stored in chilled tanks until required, and then allowed to boil (at a temperature of 90.188 K (−182.96 °C)) to release oxygen as a gas. This is widely used at hospitals due to their high usage requirements, but can also be used in other settings.
2. Compressed gas storage - The oxygen gas is compressed in a gas cylinder, which provides a convenient storage, without the requirement for refrigeration found

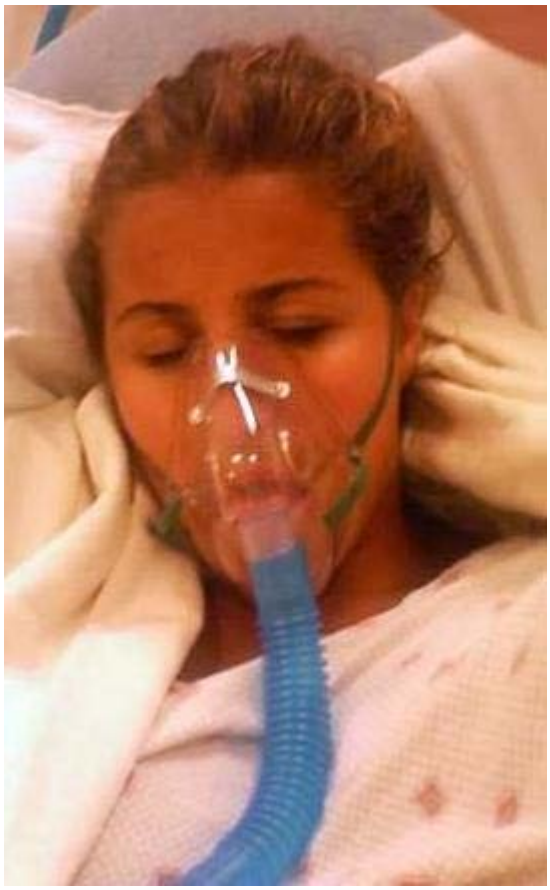
with liquid storage. Large oxygen cylinders hold 6,500 litres (230 cu ft) and can last about two days at a flow rate of 2 litres per minute. A small portable M6 (B) cylinder holds 164 or 170 litres (5.8 or 6.0 cu ft) and weighs about 1.3 to 1.6 kilograms (2.9 to 3.5 lb). These tanks can last 4–6 hours when used with a conserving regulator, which senses the patient's breathing rate and sends pulses of oxygen. Conserving regulators may not be usable by patients who breathe through their mouths.

3. Instant usage - The use of an electrically powered oxygen concentrator or a chemical reaction based unit can create sufficient oxygen for a patient to use immediately, and these units (especially the electrically powered versions) are in widespread usage for home oxygen therapy and portable personal oxygen, with the advantage of being continuous supply without the need for additional deliveries of bulky cylinders.

Delivery

Various devices are used for administration of oxygen, from whichever source. In most cases, the oxygen will first pass through a pressure regulator, used to control the high pressure of oxygen delivered from a cylinder (or other source) to a lower pressure. This lower pressure is then controlled by a flowmeter, which may be preset or selectable, and this controls the flow in a measure such as litres per minute (lpm). The typical flowmeter range for medical oxygen is between 0 and 15 lpm with some units able to obtain up to 25 liters per minute. Many wall flowmeters using a "thorpe tube" style design are able to be dialed to "flush" which is beneficial in emergency situations.

Supplemental oxygen



A patient wearing a simple face mask.

Many patients require only a supplementary level of oxygen in the room air they are breathing, rather than pure or near pure oxygen, and this can be delivered through a number of devices dependant on the situation, flow required and in some instances patient preference.

A nasal cannula (NC) is a thin tube with two small nozzles that protrude into the patient's nostrils. It can only comfortably provide oxygen at low flow rates, 2-6 litres per minute (LPM), delivering a concentration of 24-40%.

There are also a number of face mask options, such as the simple face mask, often used at between 6 and 12 LPM, with a concentration of oxygen to the patient of between 28% and 50%. This is closely related to the more controlled air-entrainment masks, also known as Venturi masks, which can accurately deliver a predetermined oxygen concentration to the trachea up to 40%.

In some instances, a partial rebreathing mask can be used, which is based on a simple mask, but featuring a reservoir bag, which increases the provided oxygen rate to 40-70% oxygen at 5 to 15 LPM.

High flow oxygen delivery

In cases where the patient requires a flow of up to 100% oxygen, a number of devices are available, with the most common being the non-rebreather mask (or reservoir mask), which is similar to the partial rebreathing mask except it has a series of one-way valves preventing exhaled air from returning to the bag. There should be a minimum flow of 10 L/min. The delivered FIO2 of this system is 60-80%, depending on the oxygen flow and breathing pattern. High flows of warmed and humidified air/oxygen blends can also be delivered via a nasal cannula, allowing the patient to continue to talk, eat and drink while still receiving the therapy.

In specialist applications such as aviation, tight fitting masks can be used, and these also have applications in anaesthesia, carbon monoxide poisoning treatment and in hyperbaric oxygen therapy

Positive pressure delivery

Patients who are unable to breathe on their own will require positive pressure to move oxygen in to their lungs for gaseous exchange to take place. Systems for delivering this vary in complexity (and cost), starting with a basic pocket mask adjunct which can be used by a basically trained first aider to manually deliver artificial respiration with supplemental oxygen delivered through a port in the mask.

Many emergency medical service and first aid personnel, as well as hospitals, will use a bag-valve-mask (BVM), which is a maleable bag attached to a face mask (or invasive airway such as an endotracheal tube or laryngeal mask airway), usually with a reservoir bag attached, which is manually manipulated by the healthcare professional to push oxygen (or air) in to the lungs. This is the only procedure allowed for initial treatment of cyanide poisoning in the UK workplace.

Automated versions of the BVM system, known as a resuscitator or pneupac can also deliver measured and timed doses of oxygen direct to patient through a facemask or airway. These systems are related to the anaesthetic machines used in operations under general anaesthesia that allows a variable amount of oxygen to be delivered, along with other gases including air, nitrous oxide and inhalational anaesthetics.

As a drug delivery route

Oxygen therapy can also be used as part of a strategy for delivering drugs to a patient, with the usual example of this being through a nebulizer mask, which delivers nebulizable drugs such as salbutamol or epinephrine into the airways by creating a vapor-mist from the liquid form of the drug.

Filtered oxygen masks

Filtered oxygen masks have the ability to prevent exhaled, potentially infectious particles from being released into the surrounding environment. These masks are normally of a closed design such that leaks are minimized and breathing of room air is controlled through a series of one-way valves. Filtration of exhaled breaths is accomplished either by placing a filter on the exhalation port, or through an integral filter that is part of the mask itself. These masks first became popular in the Toronto (Canada) healthcare community during the 2003 SARS Crisis. SARS was identified as being respiratory based and it was determined that conventional oxygen therapy devices were not designed for the containment of exhaled particles.,, Common practices of having suspected patients wear a surgical mask was confounded by the use of standard oxygen therapy equipment. In 2003, the $HiOx^{80}$ oxygen mask was released for sale. The $HiOx^{80}$ mask is a closed design mask that allows a filter to be placed on the exhalation port. Several new designs have emerged in the global healthcare community for the containment and filtration of potentially infectious particles. Other designs include the ISO-O_2 oxygen mask,the Flo_2Max oxygen mask, and the O-Mask. The use of oxygen masks that are capable of filtering exhaled particles is gradually becoming a recommended practice for pandemic preparation in many jurisdictions.

Because filtered oxygen masks use a closed design that minimizes or eliminates inadvertent exposure to room air, delivered oxygen concentrations to the patient have been found to be higher than conventional non-rebreather masks, approaching 99% using adequate oxygen flows. Because all exhaled particles are contained within the mask, nebulized medications are also prevented from being released into the surrounding atmosphere, decreasing the occupational exposure to healthcare staff and other patients.

Negative effects

Many EMS protocols indicate that oxygen should not be withheld from any patient, while other protocols are more specific or circumspect. However, there are certain situations in which oxygen therapy is known to have a negative impact on a patient's condition.

Oxygen should never be given to a patient who is suffering from paraquat poisoning unless they are suffering from severe respiratory distress or respiratory arrest, as this can increase the toxicity. (Paraquat poisoning is rare - for example 200 deaths globally from 1958–1978). Oxygen therapy is not recommended for patients who have suffered pulmonary fibrosis or other lung damage resulting from bleomycin treatment.

High levels of oxygen given to infants causes blindness by promoting overgrowth of new blood vessels in the eye obstructing sight. This is retinopathy of prematurity (ROP).

Oxygen has vasoconstrictive effects on the circulatory system, reducing peripheral circulation and was once thought to potentially increase the effects of stroke. However, when additional oxygen is given to the patient, additional oxygen is dissolved in the plasma according to Henry's Law. This allows a compensating change to occur and the

dissolved oxygen in plasma supports embarrassed (oxygen-starved) neurons, reduces inflammation and post-stroke cerebral edema. Since 1990, hyperbaric oxygen therapy has been used in the treatments of stroke on a worldwide basis. In rare instances, hyperbaric oxygen therapy patients have had seizures. However, because of the aforementioned Henry's Law effect of extra available dissolved oxygen to neurons, there is usually no negative sequel to the event. Such seizures are generally a result of oxygen toxicity, although hypoglycemia may be a contributing factor, but the latter risk can be eradicated or reduced by carefully monitoring the patient's nutritional intake prior to oxygen treatment.

Oxygen first aid has been used as an emergency treatment for diving injuries for years. Recompression in a hyperbaric chamber with the patient breathing 100% oxygen is the standard hospital and military medical response to decompression illness. The success of recompression therapy as well as a decrease in the number of recompression treatments required has been shown if first aid oxygen is given within four hours after surfacing. There are suggestions that oxygen administration may not be the most effective measure for the treatment of decompression illness and that heliox may be a better alternative.

Chronic obstructive pulmonary disease

Care needs to be exercised in patients with chronic obstructive pulmonary disease, such as emphysema, especially in those known to retain carbon dioxide (type II respiratory failure). Such patients may further accumulate carbon dioxide and decreased pH (hypercapnation) if administered supplemental oxygen, possibly endangering their lives. This is primarily as a result of ventilation–perfusion imbalance. In the worst case, administration of high levels of oxygen in patients with severe emphysema and high blood carbon dioxide reduces respiratory drive to the point of precipitating respiratory failure, and eventual death. However the risk of the loss of respiratory drive are far outweighed by the risks of withholding emergency oxygen, and therefore emergency administration of oxygen is never contraindicated. Transfer from field care to definitive care, where oxygen use can be carefully calibrated, typically occurs long before significant reductions to the respiratory drive.

A recent study has shown that titrated oxygen therapy (controlled administration of oxygen) may be more appropriate for COPD patients, and less of a danger to them. The study also showed that other, non-COPD patients, may also, in some cases, benefit more from titrated therapy. However, the results are not conclusive, and may have no statistical relevance when adjusted for proper protocol usage.

Fire risk

Highly concentrated sources of oxygen promote rapid combustion. Fire and explosion hazards exist when concentrated oxidants and fuels are brought into close proximity; however, an ignition event, such as heat or a spark, is needed to trigger combustion. Oxygen itself is not the fuel, but the oxidant. Combustion hazards also apply to

compounds of oxygen with a high oxidative potential, such as peroxides, chlorates, nitrates, perchlorates, and dichromates because they can donate oxygen to a fire.

Concentrated O_2 will allow combustion to proceed rapidly and energetically. Steel pipes and storage vessels used to store and transmit both gaseous and liquid oxygen will act as a fuel; and therefore the design and manufacture of O_2 systems requires special training to ensure that ignition sources are minimized.

Hospitals in some jurisdictions, such as the UK, now operate “no- smoking” policies, which although introduced for other reasons, supports the aim of keeping ignition sources away from medical piped oxygen. Other recorded sources of ignition of medically prescribed oxygen include candles, aromatherapy, medical equipment, cooking, and unfortunately, deliberate vandalism. Smoking pipes, cigars and cigarettes are of special concern. This does not entirely eliminate the risk of injury with portable oxygen systems, especially if compliance is poor.

Oxygen therapy while on aircraft

In the United States, most airlines restrict the devices allowed on board aircraft. As a result passengers are restricted in what devices they can use. Some airlines will provide cylinders for passengers with an associated fee. Other airlines allow passengers to carry on approved portable concentrators. However the lists of approved devices varies by airline so passengers need to check with any airline they are planning to fly on. Passengers are generally not allowed to carry on their own cylinders. In all cases, passengers need to notify the airline in advance of their equipment.

Chapter 10

Vision Therapy

Vision therapy, also known as **visual training**, **vision training**, or **visual therapy**, is a broad group of techniques aimed at correcting and improving binocular, oculomotor, visual processing, and perceptual disorders."

Historical development

Various forms of visual therapy have been used for centuries. The concept of vision therapy was introduced in the late nineteenth century for the non-surgical treatment of misaligned eyes (strabismus). This early and traditional form of vision therapy is what is now known as 'orthoptics' - although this term does not limit the work of Orthoptists who today often work beyond the realm of strabismus. Collaboration of some Eye care professionals with educators and neuroscientists produced an expansion of vision therapy into the treatment of other eye coordination (binocular) deficits as well as dysfunctions in visual focusing, perception, tracking and motor skills.

As a result of this expansion and ensuing confusion over what the term "vision therapy" includes, there is some controversy as to the use of vision therapy for individuals with learning disorders.

Current definitions in clinical practice

Vision Therapy encompasses a wide variety of non-surgical methods which some have divided into two broad categories based on their clinical acceptance and general practice by eyecare professionals:

- 1) **Orthoptic Vision Therapy**, also known as orthoptics.

It may be prescribed to patients with problems of visual related skills required for reading, eye strain, visually-induced headaches, strabismus and/or diplopia It is commonly practiced by optometrists and behavioral optometrists - however, more specialized problems are co-managed between orthoptists and ophthalmologists.

- 2) **Behavioral Vision Therapy**, or **Visual Integration Vision Therapy** (also known as behavioral or developmental optometry).

Behavioural Vision Therapy does not limit itself to disorders of the visual system. For example, Behavioral Optometrists hold that the sensitivity of a professional athlete's peripheral vision on the playing field may have enhanced responsiveness to fast moving objects with vision therapy, beyond the normal realm general improvement with practicing their sport. Ophthalmologists and orthoptists do not endorse these exercises as having clinically significant validity for improvements in vision. Usually, they see these perceptual-motor activities being in the sphere of either speech therapy, occupational therapy or physical therapy.

Orthoptic visual therapy

Orthoptics aims to treat binocular vision disorders such as strabismus, and diplopia. Key factors involved include: Eye Movement Control, Simultaneous Focus at Far, Sustaining Focus at Far, Simultaneous Focus at Near, Sustaining Focus at Near, Simultaneous Alignment at Far, Sustaining Alignment at Far, Simultaneous Alignment at Near, Sustaining Alignment at Near, Central Vision (Visual Acuity) and Depth Awareness.

Some of the exercises used are:

- Near point of convergence exercises (i.e. "pencil push-ups"),
- Base-out prism reading, stereogram cards, computerized training programs are used to improve fusional vergence.
- The wearing of convex lenses
- The wearing of concave lenses
- "Cawthorne Cooksey Exercises" also employ various eye exercises, however, these are designed to alleviate vestibular disorders, such as dizziness, rather than eye problems.
- Antisuppression exercises - this is being less commonly practiced, although occasionally it may be used.

There is widespread acceptance of orthoptic therapy indications for:

- Convergence insufficiency. Patients who experience eyestrain, "tired" eyes, or diplopia (double vision) while reading or performing other near work, and who have convergence insufficiency may benefit from orthoptic treatment. Patients whose outward drift occurs at distance rather than at near distance are less ideal candidates for treatment.
- Intermittent exotropia. This is often linked to convergence insufficiency.

Convergence insufficiency is a common binocular vision disorder characterized by asthenopia, eye fatigue and discomfort. Asthenopia may be aggravated by close work and is thought by some to contribute to reading inefficiency. In 2005, the Convergence Insufficiency Treatment Trial (CITT) published two large, randomized clinical studies

examining the efficacy of orthoptic vision therapy in the treatment of symptomatic convergence insufficiency. Although neither study examined reading efficiency or comprehension, both demonstrated that in-office vision therapy was more effective than "pencil pushups" (a commonly prescribed home-based treatment) for improving the symptoms of asthenopia and the convergence ability of the eyes. The design and results of at least one of these studies has been met with some reservation, questioning the conclusion as to whether intensive office-based treatment programs are truly more efficacious than a properly implemented home-based regimen. The CITT has since published articles validating its research and treatment protocols. Its most recent publication suggested that home-based computer therapy combined with office based vision therapy is more effective than pencil pushups or home-based computerised therapy alone for the treatment of symptomatic convergence insufficiency.

Behavioural visual therapy

Behavioral vision therapy is practiced primarily by optometrists who specialize in this field. Behavioural VT aims to treat problems including difficulties of visual attention and concentration, which may manifest themselves as an inability to sustain focus or to shift focus from one area of space to another.

This includes vision therapy for: Peripheral Vision, Color Perception, Gross Visual-Motor, Fine Visual-Motor, and Visual Perception.

Some of the exercises involve the use of:

- Marsden balls
- Rotation trainers
- Syntonics
- Balance board/beams
- Saccadic fixators
- Directional sequencers

Major optometric organizations, including the American Optometric Association, the American Academy of Optometry, the College of Optometrists in Vision Development, and the Optometric Extension Program, support the assertion that non-strabismic visual therapy does not directly treat learning disorders, but rather addresses underlying visual problems which are claimed to affect learning potential.

Major organizations, including the International Orthoptic Association and the American Academy of Ophthalmology have alternatively so far concluded that there is no current validity for clinically significant improvements in vision with Behavioural Vision Therapy, therefore they do not practice it.

Advocates cite a number of indications for the use of non-strabismic vision therapy. Some assert that poor eye tracking affects reading skills, and that improving tracking can improve reading.

Efficacy of behavioural visual therapy

In 1988, a review of 238 scientific articles was published in the *Journal of the American Optometric Association* widely defined vision therapy as "a clinical approach for correcting and ameliorating the effects of eye movement disorders, non-strabismic binocular dysfunctions, focusing disorders, strabismus, amblyopia, nystagmus, and certain visual perceptual (information processing) disorders." - and thereby did not discriminate between orthoptic and behavioural visual therapy. The paper was positive about vision therapy generally: "It is evident from the research that there is scientific support for the efficacy of vision therapy in modifying and improving oculomotor, accommodative, and binocular system disorders, as measured by standardized clinical and laboratory testing methods for patients of all ages for whom it is properly undertaken and employed."

A more recent (2005) review concluded less positively that: *"Less robust, but believable, evidence indicates visual training may be useful in developing fine stereoscopic skills and improving visual field remnants after brain damage. As yet there is no clear scientific evidence published in the mainstream literature supporting the use of eye exercises in the remainder of the areas reviewed, and their use therefore remains controversial."*

In 2006, noted neurologist Oliver Sacks published a case study about "Stereo Sue", a woman who had regained her stereo vision, absent for 48 years, after undergoing vision therapy. The article was published in *The New Yorker* magazine, which is fact-checked but not peer-reviewed, very few details were given of the exact therapies used and the article discussed only one case of stereo rehabilitation. However, the woman described by Sacks, Susan Barry, a neurobiology professor at Mt. Holyoke College, subsequently published a book, "Fixing My Gaze." The book discusses multiple case histories and details the therapy procedures and the science underlying them.

A systematic review of the literature on the effects of vision therapy on visual field defects published in 2007 concluded that it was unclear to what extent patients benefited from vision restoration therapy (VRT) as "no study has given a satisfactory answer." The authors concluded that *scanning compensatory therapy* (SCT) seemed to provide a more successful rehabilitation, and simpler training techniques, therefore they recommended SCT until the effects of VRT could be defined.

A 2008 review of the literature concluded that "there is a continued paucity of controlled trials in the literature to support behavioural optometry approaches. Although there are areas where the available evidence is consistent with claims made by behavioural optometrists ... a large majority of behavioural management approaches are not evidence-based, and thus cannot be advocated."

Other than for strabismus (such as intermittent exotropia) and convergence insufficiency, the consensus among *ophthalmologists*, *orthoptists* and *pediatricians* is that non-strabismic visual therapy lacks documented evidence of effectiveness. In 1998, the American Academy of Pediatrics, American Academy of Ophthalmology, and American

Association for Pediatric Ophthalmology and Strabismus issued a policy statement regarding the use of vision therapy specifically for the treatment of *learning problems* and *dyslexia.* According to the statement: "No scientific evidence exists for the efficacy of eye exercises ('vision therapy')... in the remediation of these complex pediatric neurological conditions." More recently, in 2004, the American Academy of Ophthalmology released a position statement asserting that there is no evidence that vision therapy retards the progression of *myopia*, no evidence that it improves visual function in those with *hyperopia* or *astigmatism,* or that it improves *vision lost through disease processes.* This was also supported by the International Orthoptic Association.

The Joint Statement mentioned above was criticised at the time by Merrill Bowan, a vision therapy enthusiast, for being biased, with the author of a rebuttal concluding "The AAP/AAO/AAPOS paper contains errors and internal inconsistencies. Through highly selective reference choices, it misrepresents the great body of evidence from the literature that supports a relationship between visual and perceptual problems as they contribute to classroom difficulties.". The author also states that the Joint Statement presents an unsupported opinion by implication that Optometrists claim that vision therapy cures the learning problem. A similar criticism could be levelled at the 2004 American Academy of Ophthalmology paper which implies that vision therapy is claimed to treat "vision lost through disease processes". There is a common theme that critics of vision therapy seem to do by placing vision therapy under the same banner with alternative therapies. By implication, the lack of evidence for the alternative therapies is cited as a lack of evidence for vision therapy. No supporting evidence is given that vision therapy is actually used to treat eye disease or vision lost through disease processes.

Some optometrists take a slightly different view. In 1999 a joint statement by the American Academy of Optometry, the American Optometric Association, the College of Optometrists in Vision Development and Optometric Extension Program Foundation reported: "Many visual conditions can be treated effectively with spectacles or contact lenses alone; however, some are most effectively treated with vision therapy....Research has demonstrated that vision therapy can be an effective treatment option for *ocular motility problems, non-strabismic binocular disorders, strabismus, amblyopia, accommodative disorders (and) visual information processing disorders.*"

Although skeptics assert that vision therapists may have a financial bias in proclaiming the efficacy of the practice, proponents and advocates of vision therapy claim that other eye professionals have a similar bias in rejecting its claims. In either case, most insurance companies do not cover vision therapy services, partly because of the lack of support for vision therapy in evidence-based literature.

Eye exercises

The eye exercises used in vision therapy can generally be divided into two groups; those employed for "strabismic" outcomes and those employed for "non-strabismic" outcomes, to improve eye health.

Some of the exercises used are

- Near point of convergence exercises (i.e. "pencil push-ups"),
- Base-out prism reading, stereogram cards, computerized training programs are used to improve fusional vergence.
- The wearing of convex lenses
- The wearing of concave lenses
- "Cawthorne Cooksey Exercises" also employ various eye exercises, however, these are designed to alleviate vestibular disorders, such as dizziness, rather than eye problems.
- Antisuppression exercises - this is no longer commonly practiced, although occasionally it may be used.

The eye exercises used in **Behavioural Vision Therapy**, also known as Developmental Optometry is practiced primarily by Behavioural Optometrists. Behavioural Vision Therapy therapy aims to treat problems including difficulties of **visual attention and concentration**, which may manifest themselves as an inability to sustain focus or to shift focus from one area of space to another.

Some of the exercises used are:

- Marsden balls
- Rotation trainers
- Syntonics
- Balance board/beams
- Saccadic fixators
- Directional sequencers

Ophthalmologists and orthoptists do not endorse these exercises as having clinically significant validity for improvements in vision. Usually they see these perceptual-motor activities being in the sphere of either speech therapy, occupational therapy or physical therapy.

Orthoptists, optometrists and ophthalmologists

Orthoptists, optometrists and ophthalmologists primarily use eye exercises that relate to strabismus treatments.

Physical therapy

- To reduce muscle contracture in an eye muscle palsy; assess action following ocular muscle surgery or botox injection.

Fusional Amplitude and Relative Fusional Amplitude training

- Designed to alleviate convergence insufficiency. The CITT study (Convergence Insufficiency Treatment Trial) was is a randomized, double blind multi-centre trial (high level of reliability) indicates that Orthoptic Vision Therapy is an effective method of treatment of convergence insufficiency (CI). Both optometry and ophthalmology were co-authors of this study.

- Designed to alleviate intermittent exotropia or other less common forms of strabismus.

The consensus among Ophthalmologists, Orthoptists and Pediatricians is that "visual training" in non-strabismic **Behavioural Vision therapy** lacks documented scientific evidence of effectiveness. Although Ophthalmologists and Orthoptists believe that exercises can improve binocular vision control, they believe it does not purely improve monocular visual acuity such as that in amblyopia (rather, occlusion is the therapy of choice), change a person's refractive error, improve general physical fitness or agility or improve intelligence. It is probable that they do not change the accommodative/convergence ratio or enable someone to develop the ability for stereopsis. It is likely that they do not change the amplitude of accommodation to postpone or delay presbyopia.

Behavioral Optometrists

Practitioners in Behavioral optometry (also known as *Functional optometrists* or *optometric vision therapists*) practice methods that have been characterized as a complementary alternative medicine practice. A review in 2000 concluded that there were insufficient controlled studies of the approach and a 2008 review concluded that "a large majority of behavioural management approaches are not evidence-based, and thus cannot be advocated."

Other forms

Do-it-yourself eye exercises are claimed by some to improve visual acuity by reducing or eliminating refractive errors. Such claims rely mainly on anecdotal evidence, and are not generally endorsed by orthoptists, ophthalmologists or optometrists.

Chapter 11

Hormone Replacement Therapy (Menopause)

Hormone replacement therapy (**HRT**) is a system of medical treatment for surgically menopausal, perimenopausal and to a lesser extent postmenopausal women. It is based on the idea that the treatment may prevent discomfort caused by diminished circulating estrogen and progesterone hormones. It involves the use of one or more of a group of medications designed to artificially boost hormone levels. The main types of hormones involved are estrogens, progesterone or progestins, and sometimes testosterone. It often referred to as "treatment" rather than therapy.

Overview

HRT is available in various forms. It generally provides low dosages of one or more estrogens, and often also provides either progesterone or a chemical analogue, called a progestin. Testosterone may also be included. In women who have had a hysterectomy, an estrogen compound is usually given without any progesterone, a therapy referred to as "unopposed estrogen therapy". HRT may be delivered to the body via patches, tablets, creams, troches, IUDs, vaginal rings, gels or, more rarely, by injection. Dosage is often varied cyclically, with estrogens taken daily and progesterone or progestins taken for about two weeks every month or two; a method called "sequentially combined HRT" or scHRT. An alternate method, a constant dosage with both types of hormones taken daily, is called "continuous combined HRT" or ccHRT, and is a more recent innovation. Sometimes an androgen, generally testosterone, is added to treat diminished libido. It may also treat reduced energy and help reduce osteoporosis after menopause.

HRT is often given as a short-term relief (often one or two years, usually less than five) from menopausal symptoms (hot flashes, irregular menstruation, fat redistribution etc.). Younger women with premature ovarian failure or surgical menopause may use hormone replacement therapy for many years, until the age that natural menopause would be expected to occur.

Attitudes towards HRT changed in 2002 following the announcement by the Women's Health Initiative of the National Institutes of Health that those receiving the treatment (Prempro) in the main part of their study had a larger incidence of breast cancer, heart attacks and strokes. The WHI findings were reconfirmed in a larger national study done in the UK, known as The Million Women Study. As a result of these findings, the number of women taking hormone treatment dropped precipitously. As a result of these findings, the Women's Health Initiative recommended that women with normal rather than surgical menopause should take the lowest feasible dose of HRT for the shortest possible time to avoid these risks.

Risks and benefits

Proprietary mixtures of conjugated equine estrogens (CEE, Premarin is one such CEE), estrogens derived from the urine of pregnant horses, have been a common prescribed form of HRT, as well as progestins. As the most common and longest-prescribed type of HRT, the majority of studies of HRT involve CEE. More recent forms of drug delivery have been researched, including suppositories, subdermal implants, skin patches and gels rather than pills or injections, which allow more local effect, lower doses, fewer side effects and a constant rather than cyclical level of hormones within the blood. Comparisons between a pill and transdermal patch suggests that when estrogens are taken orally the risks of thrombophlebitis and pulmonary embolism are increased, an effect which is not seen in with transdermal administration (this effect refers only to patches that contain estradiol for hormone replacement, and has no bearing on the patches used for birth control, which contain ethinyl estradiol). Transdermal drugs enter the bloodstream directly and unlike oral estrogens are not modified by the liver before being absorbed (modification by the liver is believed to be the reason for the increased risks). Once considered protective of the cardiovascular system, the large-scale, randomized, placebo controlled studies in the Women's Health Initiative found that conventional hormone therapy with CEE actually increased the risk of heart disease, strokes, emboli and breast cancer while offering only mild protection against osteoporosis and colorectal cancer. Unopposed estrogen (the supplementation of endogenous estrogens without a progestagen) can also result in endometrial hyperplasia, a precursor to endometrial cancer. The extensive use of high-dose estrogens for birth control in the 1970s is thought to have resulted in a significant increase in the incidence of this type of cancer.

HRT may also be effective at reversing the effects of aging on muscle and/or promoting reverse cholesterol transport (RCT) via the induction of cholesterol ABC transporters.

Women have also pursued alternative interventions which do not involve estrogen supplementation. Due to the risks and potential problems of progestins and equine estrogens, a number of alternative therapies have been presented, including lifestyle changes and phytoestrogens (plants and food supplements believed to alleviate the symptoms of menopause due to estrogen-like compounds). However, systemic reviews of the research on phytoestrogens demonstrated that these compounds are not effective. Bioidentical hormone replacement therapy has also been inaccurately promoted as a panacea and an alternative to conventional HRT, but bioidentical hormones are derived

from the same sources as nonbioidentical molecules, have been used in FDA-approved drugs for many years, lack a research base demonstrating their risks or benefits, are expected to have the same risks and benefits as conventional HRT, and frequently associated with the expensive, unnecessary and potentially dangerous practice of compounding .

Bioidentical hormone replacement therapy

Bioidentical hormone replacement therapy refers to the use of hormones that are chemically identical to those produced in a woman's body, though they are also associated with the practices of pharmaceutical compounding and saliva testing to determine, and adjust a woman's hormone levels (the latter two practices are extremely controversial - compounding has not demonstrated any benefits and presents risks of uncertain dosing, potency and possible contamination; saliva testing is considered to have no merit due to the natural fluctuations in hormone levels and the lack of support for a specific dosage of hormones being ideal). Proponents also claim that BHRT can offer advantages beyond those typical of traditional HRT, though there is no evidence to support these claims. The United States Food and Drug Administration states that BHRT is expected to present the same risks and benefits of non-bioidentical HRT, but that traditional products have been researched to quantify these risks and benefits, and are produced by manufacturers with stringent purity and potency standards.

Results of the WHI hormone replacement therapy studies

Clinical medical practice changed rapidly and dramatically with the results of the two parallel WHI studies of postmenopausal HRT. Prior studies were much smaller, and many were studies of women who were electively taking hormones. This self-selected group tended to be composed of women who were more health-conscious, which was a possible factor to explain why these women tended to be healthier than the average. The WHI studies were the first large, double-blind, placebo-controlled clinical trials of HRT in healthy, postmenopausal women. The WHI estrogen-plus-progestin trial and estrogen-alone trial were both halted early (in July 2002 and February 2004 respectively) because preliminary study results indicated that the health risks of the conjugated equine estrogen and progestin exceeded benefits.

The first report on the halted WHI estrogen-plus-progestin study came out in July 2002. It followed over 16 000 women for an average of 5.2 years, half of which taking a placebo, the other half taking PremPro, a combination of the progestin medroxyprogesterone acetate and conjugated equine estrogens. The study found statistically significant increases in rates of breast cancer, coronary heart disease, strokes and pulmonary emboli. The study also found statistically significant decreases in rates of hip fracture and colorectal cancer. "A year after the study was stopped in 2002, an article was published indicating that estrogen plus progestin also increases the risks of dementia." The conclusion of the study was that the HRT combination presented risks that outweighed its measured benefits. The results were almost universally reported as

risks and problems associated with HRT in general, rather than with PremPro, the specific proprietary combination of conjugated equine estrogen and progestin studied.

The increase in risks of coronary heart disease in the PremPro arm of the study varied according to age and years since the onset of menopause. Women aged 50 to 59 using HRT showed a small trend towards lower risk of coronary heart disease, as did women who were within five years of the onset of menopause.

The adverse cardiovascular outcomes may only apply to oral dosing with the progestin and equine estrogens in Prempro, while other types of HRT such as topical estradiol and estriol may not produce the same risks. Results from other studies suggest that when estrogen is administered orally, liver function is altered and the risk of blood clots is increased.

The WHI preliminary results in 2004 found a non-significant trend in the estrogen-alone clinical trial towards a reduced risk of breast cancer and a 2006 update concluded that use of estrogen-only HRT for 7 years does not increase the risk of breast cancer in postmenopausal women who have had a hysterectomy. The results of the WHI estrogen-alone trial suggest that the progestin used in the WHI estrogen-plus-progestin trial increased the risk for breast cancer above that associated with estrogen alone.

After the increased clotting found in the first WHI results was reported in 2002, a large number of women who had been taking the proprietary mixtures of equine estrogens and progestins studied (Prempro) ceased filling their prescriptions. The number of Prempro prescriptions filled was abruptly cut almost in half. A number of women started taking alternatives to Prempro, such as bioidentical hormones. A sharp drop in breast cancer rates was observed following these changes, and held steady in subsequent years.

Recent findings

According to a 2007 presentation at an American Academy of Neurology meeting, hormone therapy taken soon after menopause may help protect against dementia, even though it raises the risk of mental decline in women who do not take the drugs until they are older. Dementia risk was 1% in women who started HRT early, and 1.7% in women who didn't, (e.g. women who didn't take it seem to have had—on average—a 70% higher relative risk of dementia). This is consistent with research that hormone therapy improves executive and attention processes in postmenopausal women. It is also supported by research upon monkeys that were given ovariectomies to imitate the effect of menopause and then estrogen therapies. This showed replacement treated compared to nontreated monkeys had long term improved prefrontal cortex executive abilities on the Wisconsin card sort task.

Another recent randomized controlled trial found HRT may actually prevent the development of heart disease and reduce the incidence of heart attack in women between 50 and 59, but not for older women. The mechanism may have something to do with the contradictory effects of increasing propensity for clotting, versus improving both "good"

and "bad" cholesterol concentrations in the blood (which would have a protective effect). Followup studies are being performed which are intended to confirm these findings. The increased risk of breast cancer remains.

A recent large well-designed randomized controlled trial recently showed that increased breast cancer risk applies only to those women who take progesterone analogues (as was done in the WHI) but not to those taking progesterone itself

Contraindications

Absolute contraindications

- Undiagnosed vaginal bleeding
- Severe liver disease
- Pregnancy
- Coronary artery disease (CAD)
- Venous thrombosis
- Well-differentiated and early endometrial cancer (once treatment for the malignancy is complete, is no longer an absolute contraindication.) Progestins alone may relieve symptoms if the patient is unable to tolerate estrogens.

Relative contraindications

- Migraine headaches
- Personal history of breast cancer
- History of uterine fibroids
- Atypical ductal hyperplasia of the breast
- Active gallbladder disease (cholangitis, cholecystitis)

Side effects

Common symptoms

- Headache
- Upset stomach, stomach cramps or bloating
- Diarrhea
- Appetite and weight changes
- Changes in sex drive or performance
- Nervousness
- Brown or black patches on the skin
- Acne
- Swelling of hands, feet, or lower legs due to fluid retention
- Changes in menstrual flow
- Breast tenderness, enlargement, or discharge
- Sudden difficulty wearing contact lenses

Uncommon symptoms

- Double vision
- Severe abdominal pain
- Yellowing of skin or eyes
- Severe depression
- Unusual bleeding
- Loss of appetite
- Skin rash
- Laxitude
- Fever
- Dark-colored urine
- Light colored stool
- Chorea

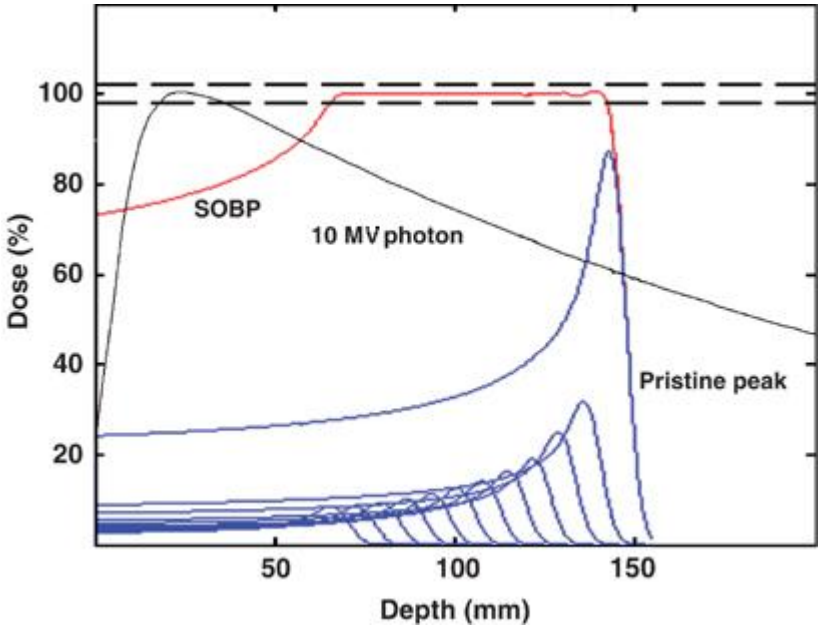
Chapter 12

Proton Therapy

2005 image of the control panel of the synchrocyclotron at the Orsay proton therapy center

Proton therapy is a type of particle therapy which uses a beam of protons to irradiate diseased tissue, most often in the treatment of cancer. The chief advantage of proton therapy is the ability to more precisely localize the radiation dosage when compared with other types of external beam radiotherapy.

Description



In a typical treatment plan for proton therapy the red line representing the spread out Bragg peak (SOBP) is the therapeutic radiation distribution. The SOBP is the sum of several pristine Bragg peaks (blue lines) at staggered depths. The depth-dose plot of a 10 MV x-ray (photon) beam is provided for comparison.

Proton therapy is a type of external beam radiotherapy using ionizing radiation. During treatment, a particle accelerator is used to target the tumor with a beam of protons. These charged particles damage the DNA of cells, ultimately causing their death or interfering with their ability to reproduce. Cancerous cells, because of their high rate of division and their reduced ability to repair damaged DNA, are particularly vulnerable to attack on their DNA.

Due to their relatively large mass, protons have little lateral side scatter in the tissue; the beam does not broaden much, stays focused on the tumor shape and delivers small dose side-effects to surrounding tissue. All protons of a given energy have a certain range; very few protons penetrate beyond that distance. Furthermore, the dose delivered to tissue is maximum just over the last few millimeters of the particle's range; this maximum is called the Bragg peak.

To treat tumors at greater depths, the proton accelerator must produce a beam with higher energy, typically given in eV or electron volts. Tumors closer to the surface of the body are treated using protons with lower energy. The accelerators used for proton therapy typically produce protons with energies in the range of 70 to 250 MeV (Mega electron Volts: million electron Volts). By adjusting the energy of the protons during application of treatment, the cell damage due to the proton beam is maximized within the tumor itself. Tissues closer to the surface of the body than the tumor receive reduced radiation,

and therefore reduced damage. Tissues deeper within the body receive very few protons so that the dosage becomes immeasurably small.

In most treatments, protons of different energies with Bragg peaks at different depths are applied to treat the entire tumor. These Bragg peaks are shown as blue lines in the figure to the left. The total radiation dosage of the protons is called the *Spread-Out Bragg Peak* (SOBP), shown as a red line in figure to the left. It is important to understand that, while tissues *behind* or *deeper than* the tumor receive no radiation from proton therapy, the tissue *in front of* or *shallower than* the tumor receive radiation dosage based on the SOBP.

History

The first suggestion that energetic protons could be an effective treatment method was made by Robert R. Wilson in a paper published in 1946 while he was involved in the design of the Harvard Cyclotron Laboratory (HCL). The first treatments were performed with particle accelerators built for physics research, notably Berkeley Radiation Laboratory in 1954 and at Uppsala in Sweden in 1957. In 1961, a collaboration began between HCL and the Massachusetts General Hospital (MGH) to pursue proton therapy. Over the next 41 years, this program refined and expanded these techniques while treating 9,116 patients before the Cyclotron was shut down in 2002. The world's first hospital-based proton therapy center was built in 1990 at the Loma Linda University Medical Center (LLUMC) in Loma Linda, California. Later, The Northeast Proton Therapy Center at Massachusetts General Hospital was brought online, and the HCL treatment program was transferred to it during 2001 and 2002.

Application

The types of treatments for which protons are used can be separated into two broad categories. The first are those for disease sites that favor the delivery of higher doses of radiation, i.e. dose escalation. In some instances dose escalation has been shown to achieve a higher probability of "cure" (i.e. local control) than conventional radiotherapy. These include (but are not limited to) uveal melanoma (ocular tumors), skull base and paraspinal tumors (chondrosarcoma and chordoma), and unresectable sarcomas. In all these cases proton therapy achieves significant improvements in the probability of local control over conventional radiotherapy.

The second broad class are those treatments where the increased precision of proton therapy is used to reduce unwanted side effects, by limiting the dose to normal tissue. In these cases the tumor dose is the same as that used in conventional therapy, and thus there is no expectation of an increased probability of curing the disease. Instead, the emphasis is on the reduction of the integral dose to normal tissue, and thus a reduction of unwanted effects. Two prominent examples are pediatric neoplasms (such as medulloblastoma) and prostate cancer. In the case of pediatric treatments there is convincing clinical data showing the advantage of sparing developing organs by using protons, and the resulting reduction of long term damage to the surviving child.

In the case of prostate cancer the issue is not so clear. Some published studies found a reduction in long term rectal and genitio-urinary damage when treating with proton rather than photon also known as X-ray or gamma ray therapy. Others showed the difference is small, and limited to cases where the prostate is particularly close to certain anatomical structures. The relatively small improvement found may be the result of inconsistent patient set-up and internal organ movement during treatment, which offsets most of the advantage due to increased precision. One source suggests that dose errors around 20% can result from motion errors of just 2.5 mm, and another that prostate motion is between 5–10 mm.

However, the number of cases of prostate cancer diagnosed each year far exceeds those of the other diseases referred to above, and this has led some, but not all, facilities to devote a majority of their treatments slots to prostate treatments. For example two hospital facilities devote roughly 65% and 50% of their proton treatment capacity to prostate cancer, while a third devotes only 7.1%

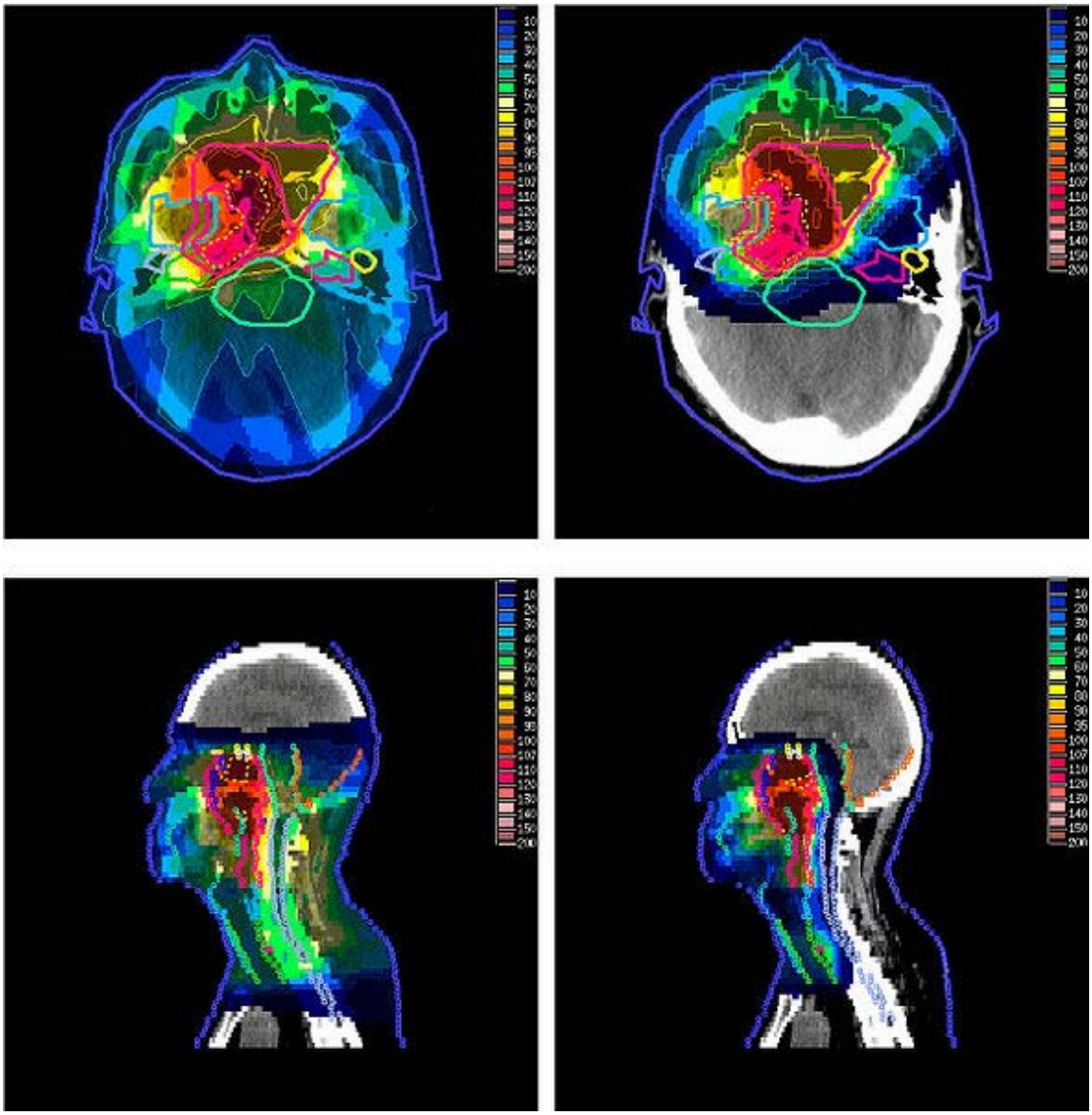
Current overall world wide numbers are hard to compile, but one example in the literature shows that in 2003 roughly 26% of proton therapy treatments world wide were for prostate cancer. Proton therapy for ocular (eye) tumors is a special case since this treatment requires only a comparably low energy (about 70 MeV). Owing to this low energy requirement, some particle therapy centers only treat ocular tumors. Proton, or more generally, Hadron therapy of tissue close to the eye affords sophisticated methods to assess the alignment of the eye that can vary significantly from other patient position verification approaches in image guided particle therapy . Position verification and correction have to ensure that sensitive tissue like the optic nerve is spared from the radiation in order to preserve the patient's vision.

Comparison with other treatment options

The issue of when, whether, and how best to apply this technology is controversial. As of 2009 it is not yet known whether proton therapy yields better clinical outcomes than other types of radiation therapy for people with many common cancers. Proton therapy is far more expensive than conventional therapy. It requires a large capital investment (roughly $100M to $150M) for 2009 technology.

Preliminary results from a three-year 2009 study, including high dose treatments, show very few side effects.

X-ray radiotherapy



Irradiation of nasopharyngeal carcinoma by photon(X-ray) therapy (left) and proton therapy (right)

The figure at the right of the page shows how beams of x-rays (IMRT) left frame and beams of protons right frame, of different energies, penetrate human tissue. A tumor with a sizable thickness is covered by the IMPT spread out Bragg peak (SOBP) shown as the red lined distribution in the figure. The SOBP is an overlap of several pristine Bragg peaks (blue lines) at staggered depths.

X-ray therapy may be described as having more "skin sparing potential" than proton therapy: x-ray radiation at the skin and at very small depths is lower than for proton therapy. One study estimates that passively scattered proton fields have a slightly higher

entrance dose at the skin (~75%) compared to therapeutic megavoltage (MeV) photon beams (~60%). X-ray radiation dose falls off gradually, while tissues deeper in the body than the tumor receive essentially no radiation during proton therapy. Thus, x-ray therapy causes less damage to the skin and surface tissues, and proton therapy causes less damage to tissues beyond the target.

Surgery

The decision to use surgery or proton therapy (or in fact any radiation therapy) is based on the tumor type, stage, and location. In some instances surgery is superior (e.g. cutaneous melanoma), in some instances radiation is superior (e.g. skull base chondrosarcoma), and in some instances they are comparable (e.g. prostate cancer). In some instances, they are used together (e.g. rectal cancer or early stage breast cancer). The benefit of external beam proton radiation lies in the dosimetric difference from external beam x-ray radiation and brachytherapy in cases, where the use of radiation therapy is already indicated, rather than as a direct competition with surgery.

Side effects and risks

Proton therapy is a type of external beam radiotherapy, and shares risks and side effects of other forms of radiation therapy. Proton therapy has been in use for over 40 years, and is a mature treatment technology. However, as with all medical knowledge, understanding of the interaction of radiation (proton, X-ray, etc.) with tumor and normal tissue is still imperfect.

Treatment centers

As of April 2010, there were a total of 29 proton therapy centers in Canada, China, England, France, Germany, Italy, Japan, Korea, Russia, South Africa, Sweden, Switzerland, and USA; and more than 67000 patients had been treated. One hindrance to universal use of the proton in cancer treatment is the size and cost of the cyclotron or synchrotron equipment necessary. Several industrial teams are working on development of comparatively small accelerator systems to deliver the proton therapy to patients. Among the technologies being investigated are Superconducting synchrocyclotrons (also known as FM Cyclotrons), ultra-compact Synchrotrons and Dielectric wall accelerators

Chapter 13

Fluoride Therapy

Fluoride therapy is the delivery of fluoride to the teeth topically or systemically in order to prevent tooth decay (dental caries) which results in cavities. Most commonly, fluoride is applied topically to the teeth using gels, varnishes, toothpaste/dentifrices or mouth rinse. Systemic delivery involves fluoride supplementation using water, salt, tablets or drops which are swallowed. Tablets or drops are rarely used where public water supplies are fluoridated.

Benefits

Fluoridation is widely, but not universally, accepted by dentists as being useful. The U.S. Center for Disease Control lists water fluoridation as one of the "ten greatest public health achievements of the 20th century." It is therefore understandable that fluoride therapy would be commonly practiced and in many modalities. Many types of fluoride therapies are known, ranging from at-home therapies (use of fluoridated toothpaste) to professionally administered, such as topical fluorides provided by dental offices, to publicly sponsored fluoridation of water or other commonly ingested materials such as salt. At-home therapies can be further divided into over-the-counter (OTC) and prescription strengths. The fluoride therapies, whether OTC or PATF, are categorized by application – dentifrices, mouthrinses, gels/ foams, varnishes, dietary fluoride supplements, and water fluoridation.

Mechanism

All fluoridation methods provide low concentrations of fluoride ions in saliva, thus exerting a topical effect on the plaque fluid. Fluoride combats the decay primarily by the formation Fluorapatite via remineralization of enamel. The fluoride ions reduce the rate of tooth enamel demineralization, and increase the rate of remineralization of the early stages of cavities. Fluoride exerts its major effect by this demineralization and remineralization cycle. Fluoride also affects the physiology of dental bacteria, although its effect on bacterial growth does not seem to be relevant to cavity prevention. Fluoride has minimal effect on cavities after it is swallowed. Technically, fluoride does not

prevent cavities but rather controls the rate at which they develop. Although fluoride is the only well-documented agent with this property, it has been suggested that also adding some calcium to the water would reduce cavities further.

Delivery

Water fluoridation

Water fluoridation is the controlled addition of fluoride to a public water supply in order to reduce tooth decay. Its use in the U.S. began in the 1940s, following studies of children in a region where water is naturally fluoridated. It is now used for about two-thirds of the U.S. population on public water systems and for about 5.7% of people worldwide. Although the best available evidence shows no association with adverse effects other than fluorosis, most of which is mild, water fluoridation has been contentious for ethical, safety, and efficacy reasons, and opposition to water fluoridation exists despite its support by public health organizations. As mentioned, fluoride primarily only helps teeth when it is in the mouth. After it is swallowed, it has minimal effect.

A 2000 systematic review of water fluoridation's effectiveness found that fluoridation was associated with a decreased proportion of children with cavities (the median of mean decreases was 14.6%, the range −5% to 64%), and with a decrease in decayed, missing, and filled primary teeth (the median of mean decreases was 2.25 teeth, the range 0.5 to 4.4 teeth). A more comprehensive 2007 review which used the 2000 review for its water fluoridation efficacy conclusions affirmed this result.

Toothpaste

Most toothpaste today contains 0.32% (1450 ppm) fluoride, usually in the form of sodium fluoride or sodium monofluorophosphate (MFP); 100 g of toothpaste containing 0.76 g MFP equates to 0.1 g fluoride.

Prescription strength fluoride toothpaste generally contains 1.1% (4,950 ppm) sodium fluoride toothpaste. This type of toothpaste is used in the same manner as regular toothpaste. It is well established that 1.1% sodium fluoride is safe and effective as a preventive of caries. This prescription dental cream is used up to three times daily in place of regular toothpaste.

Mouth rinses

The most common fluoride compound used in mouth rinse is sodium fluoride. Over-the-counter solutions of 0.05% sodium fluoride (225 ppm fluoride) for daily rinsing are available for use. Fluoride at this concentration is not strong enough for people at high risk for caries.

Prescription mouth rinses are more effective for those at high risk for caries, but are usually counterindicated for children, especially in areas with fluoridated drinking water.

However, in areas without fluoridated drinking water, these rinses are sometimes prescribed for children.

Gels/foams

Gels and foams are used for individuals who are at high risk for caries, orthodontic patients, patients undergoing head and neck radiation, patients with decreased salivary flow, and children whose permanent molars should, but cannot, be sealed.

The gel or foam is applied through the use of a mouth tray, which contains the product. The tray is held in the mouth by biting. Application generally takes about four minutes, and patients should not rinse, eat, smoke, or drink for at least 30 minutes after application.

Some gels are made for home application, and are used in a manner similar to toothpaste. The concentration of fluoride in these gels is much lower than professional products.

Varnish

Fluoride varnish has practical advantages over gels in ease of application, a non-offensive taste, and use of smaller amounts of fluoride than required for gel applications. Varnish is intended for the same group of patients as the gels and foams. There is also no published evidence as of yet that indicates that professionally applied fluoride varnish is a risk factor for enamel fluorosis. The varnish is applied with a brush and sets within seconds.

Slow-release devices

Devices that slowly release fluoride can be implanted on the surface of a tooth, typically on the side of a molar where it is not visible and does not interfere with eating. The two main types are copolymer membrane and glass bead. These devices are effective in raising fluoride concentrations and in preventing cavities, but they have problems with retention rates, that is, the devices fall off too often.

Dietary supplements

Dietary fluoride supplements in the form of tablets, lozenges, or liquids (including fluoride-vitamin preparations) are used primarily for children in areas without fluoridated drinking water. The evidence supporting the effectiveness of this treatment for primary teeth is weak. The supplements prevent cavities in permanent teeth. A significant side effect is mild to moderate dental fluorosis.

Indications for fluoride therapy

The individual's risk factors and the reason for treatment will determine which method of fluoride delivery is used. Consult with a dentist before starting any treatment.

- white spots
- Moderate to high risk patients for developing decay
- Active decay
- Orthodontic treatment
- Additional protection if necessary for children in areas without fluoridated drinking water
- To reduce tooth sensitivity
- Protect root surface
- Decreased salivary flow
- Institutionalized patients

Health risks

Consumption of large amounts of fluoride can lead to fluoride poisoning and death, but the amounts of fluoride amount to several ounces for an adult. Chronic intake and topical exposure may cause dental fluorosis, and excess systematic exposure can lead to systemic effects such as skeletal fluorosis. Young children are at risk for receiving excess fluoride, and the ADA has recently issued an interim guidance on their fluoride consumption.

Overdose

In 1974 a 3-year old child swallowed 45 milliliters of 2% fluoride solution, estimated to be triple the fatal amount, and then died. The fluoride was administered during his first visit to the dentist, and the dental office was later found liable for the death.

Fluorosis

Most fluorosis is mild and cosmetic, but the chance of more severe fluorosis increases with exposure. A recent report by National Research Council (NRC) states that severe dental fluorosis can be considered a "toxic effect" which increases the prevalence of caries (106), but fluorosis this severe is not expected with the normal use of fluoride therapy.

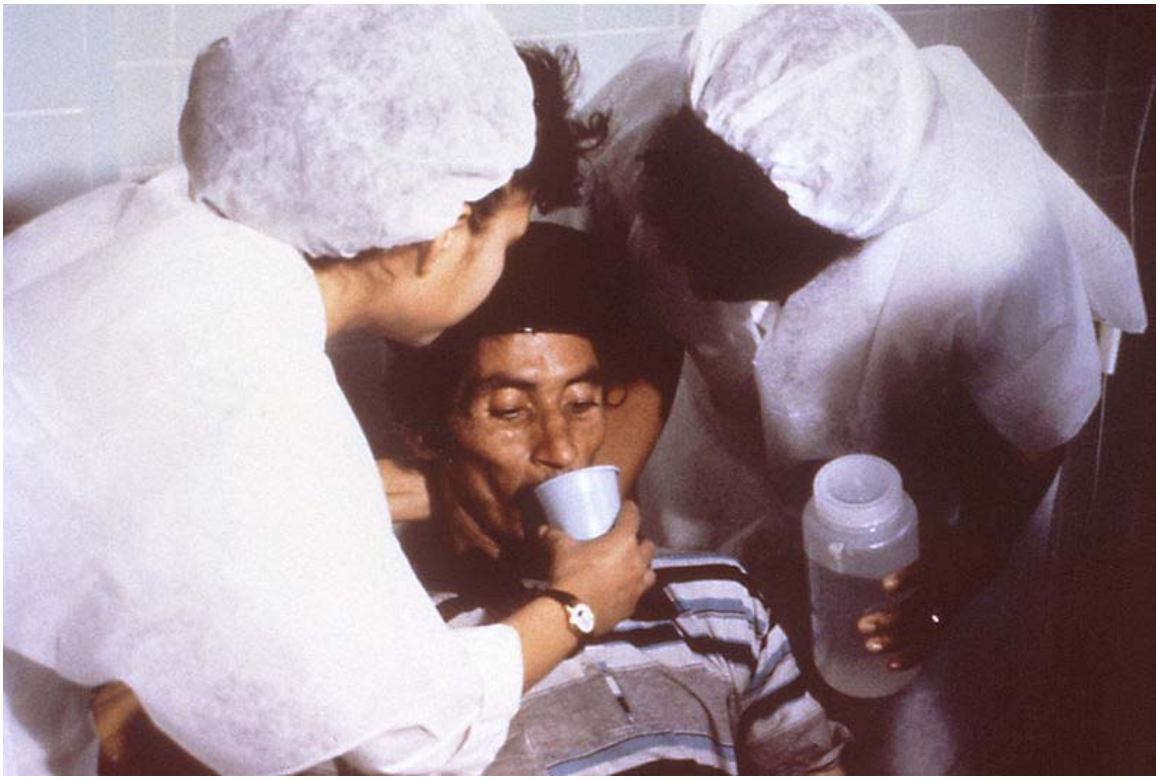
Fluoride conversion chart

APF (10)(%)(1000)	ppm
1.0%	10,000
1.23%	12,300
NaF (4.5)(%)(1000)	ppm
0.05%	225
0.20%	900
0.44%	1,980
1.0%	4,500
1.1%	4,950
2.0%	9,000
5.0%	22,500
SnF_2 (2.4)(%)(1000)	ppm

0.40%	**960**
0.63%	**1,512**

Chapter 14

Oral Rehydration Therapy



Nurses encouraging a patient to drink an oral rehydration solution to combat dehydration caused by cholera.

Oral rehydration therapy (**ORT**) is a simple treatment for dehydration associated with diarrhea, particularly gastroenteritis or gastroenteropathy, such as that caused by cholera or rotavirus. ORT consists of a solution of salts and sugars which is taken by mouth. It is used around the world, but is most important in the developing world, where it saves millions of children a year from death due to diarrhea - the second leading cause of death in children under five (the first is pneumonia).

Definition

The definition of ORT has changed over time, broadening in scope and encompassing a definition of a specific therapy appropriate for rehydration. Initially, in the early 1980s, ORT was defined only as the official solution prescribed by the WHO/UNICEF. It was later changed in 1988 to also encompass recommended home fluids, as it was noted that access to the official preparation was not always readily available. It was amended once again in 1988 to include continued feeding as appropriate management. In 1991, the definition was changed to define ORT as any increase in administered fluids. The final change came in 1993, and is the definition used today, which states that ORT is an increase in administered fluids and continued feeding.

Administration

Pouring of an ORS sachet into a bottle

According to current WHO/UNICEF guidelines, ORT should begin at home with "home fluids" or a home-prepared "sugar and salt" solution at the first sign of diarrhea to prevent dehydration. Feeding should be continued at all times. After initial fluid volume has been restored, the regimen should be switched to official preparations of *oral rehydration salts* (ORS) at the appropriate dosing times to maintain adequate hydration and proper electrolyte balance.

During the home-prepared stage, care should be taken to select the proper type of fluid to administer. The fluids given must contain both sugar and salt in the proper amounts. Liquids without both these components must be avoided. Too little of either can be ineffective and/or detrimental. Liquids without salt can lead to low body salt

(hyponatremia) because the diarrheal stool contains salt and must be replenished. Additionally, sugar must also be present in the administered fluid because salt absorption is coupled with sugar in the intestine via the SGLT1 transporter.

Appropriate drinks to administer during the home-prepared stage include official ORSs, salted rice water, salted yogurt-based drinks, and vegetable or chicken soup with salt. Clean water should always be used when preparing a solution. Drinks to be avoided include soft drinks, sweetened fruit drinks, sweetened tea, coffee, and medical tea infusions with diuretic effects due to high sugar content and/or caffeine. In addition, drinks with a high concentration (osmolarity) of sugar can worsen diarrhea as they draw water out of the body and into the intestine because of their hypertonicity.

If dehydration ensues even when ORT is begun with a home-prepared solution, if available, a qualified health professional should manage further rehydration with ORS to ensure proper electrolyte balance and to facilitate rapid rehydration, and treatment of the underlying cause of dehydration if appropriate.

Availability

By definition, ORT is available anywhere that adequate nutrition is available. ORS, on the other hand, is typically packaged in pre-measured sachets that are ready to be mixed in with water (generally 1L). These are available via commercial manufacturers or supplied by local/regional governments or relief agencies such as UNICEF. In 1996 alone, UNICEF distributed 500 million sachets of ORS to over 60 developing nations. Among the commercial suppliers, many variations in formulations abound and there is no restriction as to what formulation can be marketed as ORS. As such, some vendors include extra sugar or other flavoring to make the product more palatable, popular examples in the US being the various flavors and formulations of Pedialyte.

Where ORS sachets are not available, home-prepared solutions are typically used. Many recipes exist, but most are some easy-to-remember combination of water, sugar, and salt. An example of such is 1 level teaspoon of salt, 8 level teaspoons of sugar, and (optionally) 4 ounces (113g) of orange juice; mixed into 1 liter of clean water. If the water source is questionable, it should be boiled for 10 minutes and allowed to cool before mixing the solution.

WHO/UNICEF definition of ORS

Concentrations of ingredients in reduced osmolarity ORS

Ingredient	g/L	Molecule/ion	mmol/L
sodium chloride (NaCl)	2.6	sodium	75
glucose, anhydrous ($C_6H_{12}O_6$)	13.5	glucose	75
potassium chloride (KCl)	1.5	potassium	20

		chloride	65
trisodium citrate, dihydrate $Na_3C_6H_5O_7 \cdot 2H_2O$	2.9	citrate	10

The WHO and UNICEF jointly maintain the official guidelines for the contents of reduced osmolarity ORS packets. These guidelines are used by manufacturers of commercial ORS packets that are available for purchase and were last updated in 2006. The reduced osmolarity ORS has a total osmolarity of 245 mmol/L.

Zinc supplementation

There is an additional recommendation of zinc supplementation for the management of diarrheal disease in addition to ORS, particularly for pediatric patients. For children under five, zinc supplementation significantly reduces the severity and duration of diarrhea and is strongly recommended as a supplement with ORS for dehydrated children. Preparations are available as a zinc sulfate solution for adults, a modified solution for children, and also a tablet form for children.

Switch to reduced osmolarity ORS

In 2003, WHO/UNICEF changed the ORS formula to a reduced osmolarity version from what it had been recommending for over two decades prior. This change was in response to numerous studies that showed that the standard ORS formula was ineffective in reducing diarrheal stool output compared to other solutions, including rice water. Additionally, further studies showed that a reduced osmolarity solution not only decreased stool output, but also resulted in less vomiting and fewer unscheduled intraveneous therapy cases. Although UNICEF certifies reduced osmolarity ORS for all forms of dehydration, at least one study cautions that for high stool output cholera-based diarrhea, reduced osmolarity ORS may not sufficiently replenish electrolyte levels, leading to hyponatremia. Though the actual consequence of this appeared negligible, further study was recommended.

The change reduced the osmolarity of the ORS from 311 mmol/L to 245 mmol/L. The ingredients reduced in concentration were glucose and sodium chloride. Potassium and citrate concentrations remained the same. The benefits of the reduced osmolarity ORS are reducing stool volume by about 25%, reducing vomiting by nearly 30%, and reducing the need for unscheduled intraveneous therapy by 33%.

Physiological basis

Fluid from the body is normally pumped into the intestinal lumen during digestion. This fluid is typically isosmotic with blood because it contains a high concentration of sodium (approx. 142 mEq/L). A healthy individual will secrete 20-30 grams of sodium per day via intestinal secretions. Nearly all of this is reabsorbed by the intestine, helping to maintain constant sodium levels in the body (homeostasis).

Because there is so much sodium secreted by the intestine, without intervention, heavy continuous diarrhea can be a very dangerous and potentially life-threatening condition within hours. This is because liquid secreted into the intestinal lumen during diarrhea passes through the gut so quickly that very little sodium is reabsorbed, leading to very low sodium levels in the body (severe hyponatremia). This is the motivation for sodium and water replenishment via ORT.

Sodium absorption via the intestine occurs in two stages. The first is at the outermost cells (intestinal epithelial cells) at the surface of the intestinal lumen. Sodium passes into these outermost cells by co-transport facilitated diffusion (symport diffusion) via the SGLT1 protein. From there, sodium is pumped out of the cells (basal side) and into the extracellular space by active transport via the sodium potassium pump.

The co-transport of sodium into the epithelial cells via the SGLT1 protein requires glucose or galactose. Two sodium ions and one molecule of glucose/galactose are transported together across the cell membrane through the SGLT1 protein. Without glucose or galactose present, intestinal sodium will not be absorbed. This is the reason glucose is included in ORSs. For each cycle of the transport, hundreds of water molecules move into the epithelial cell, and this brings about the rehydration.

History

Prescriptions from the ancient Indian physician Sushruta date back over 2500 years with treatment of acute diarrhea with rice water, coconut juice, and carrot soup. However, this knowledge did not carry over to the Western world, as dehydration was found to be the major cause of death secondary to the 1829 cholera pandemic in Russia and Western Europe. In 1831, William Brooke O'Shaughnessy noted the loss of water and salt in the stool of cholera patients and prescribed intravenous fluid therapy (IV) to compensate. The results were remarkable, as patients who were on the brink of death from dehydration recovered. The mortality rate of cholera dropped from 70% to 40% with the use of hypertonic IV solutions. IV fluid replacement became entrenched as the standard of care for moderate/severe dehydration for over a hundred years. ORT replaced it with the support of several independent key advocates that ultimately convinced the medical community of the efficacy of ORT.

In the late 1950s, ORT was prescribed by Dr. Hemendra Nath Chatterjee in India for cholera patients. Although his findings predate physiological studies, his results failed to gain credibility and recognition because they did not provide scientific controls and detailed analysis. Credit for discovery that in the presence of glucose, sodium and chloride became absorbable during diarrhea (in cholera patients) is typically ascribed to Dr. Robert A. Phillips. However, early attempts to translate this observation into an effective oral rehydration solution failed, due to incorrect solution formula and inadequate methodology.

In the early 1960s, biochemist Robert K. Crane discovered the sodium-glucose cotransport as the mechanism for intestinal glucose absorption. Around the same time,

others showed that the intestinal mucosa was not disrupted in cholera, as previously thought. These findings were confirmed in human experiments, where it was first shown that a glucose-saline oral therapy solution administered in quantities matching measured diarrhea volumes was effective in significantly decreasing the necessity for IV fluids by 80%. These results helped establish the physiological basis for the use of ORT in clinical medicine.

The events surrounding the Bangladesh Liberation War in 1971 convinced the world of the effectiveness of ORT. As medical teams ran out of intravenous fluids to treat the spreading cholera epidemic, Dr. Dilip Mahalanabis instructed his staff to distribute oral rehydration salts (ORS) to the 350,000 people in refugee camps. Over 3,000 patients with cholera were treated, and the death rate was only 3.6%, compared to the typical 30% seen in intravenous fluid therapy. The fact that ORT was delivered primarily by family members instead of trained staff across such a large population in an emergency fashion was demonstrative proof of the utility of ORT against cholera.

Between 1980 and 2006, ORT decreased the number of worldwide deaths from 5 million a year to 3 million a year. Death from diarrhea was the leading cause of infant mortality in the developing world until ORT was introduced. It is now the second leading cause of mortality for children under 5, accounting for 17% of all deaths, second only to pneumonia, at 19%. Its remarkable success has led to naming the discovery of its underlying physiological basis as "potentially the most important medical advance [of the 20th] century." ORT is part of UNICEF's GOBI program, a low cost program to increase child survival in developing countries, including growth monitoring, ORT, breastfeeding, and immunization. Despite the success and effectiveness of ORT, its uptake has recently slowed and even reversed in some developing countries. This raises concerns for increased mortality from diarrhea and highlights the need for effective community-level behavioral change and global funding and policy.

The individuals and organizations involved in the development of ORT have been recognized widely. The 2001 Gates Award for Global Health was awarded to the Centre for Health and Population Research, located in Dhaka, Bangladesh, for its role in the development of ORT. In 2002, the first Pollin Prize for Pediatric Research was awarded to Dr. Norbert Hirschhorn, Dr. Dilip Mahalanabis, Dr. David Nalin, and Dr. Nathaniel F. Pierce for their contributions in the discovery and implementation of ORT. For promoting the use of ORT, the 2006 Prince Mahidol Award was awarded to Dr. Richard Alan Cash, Dr. David Nalin, and Dr. Dilip Mahalanabis in the field of public health; and to Dr. Stanley G Schultz in the field of medicine.