have doubtless been omitted many references and much information of value, a circumstance almost inevitable for various reasons, among them the difficulty sometimes surrounding the securing of the scientific journals of the various countries and an inability to take in the full significance of developments in parasitology across the distances separating the different Republics. This serves to emphasize the necessity of creating closer contacts among all the centers and scientific workers of our countries. The world conflict just ended brought, as do all great upheavals, some good along with its host of evils, one of these benefits being the focusing of our minds on our continental problems, our natural resources, our diseases, and our investigators and investigations, causing us to think of the Western Continent as a whole. Let us hope that the solidarity born of war shall be maintained and intensified with peace, creating an uninterrupted interchange of information, publications, materials, students, professors, and investigators, crossing and recrossing the hemisphere like tireless shuttles weaving, with the slender thread of Science, the tapestry of mutual understanding, appreciation, and respect, from one end of the New World to the other.

PROGRESS IN THERAPEUTICS

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The most conspicuous feature of present-day therapeutics is undoubtedly its extraordinary fluidity and instability, which make difficult for the practicing physician the proper and well-informed use and understanding of the new resources, and even a mere acquaintance with the newer concepts. In every branch of therapeutics there is the same bewildering succession of means and concepts. Naturally, medical science is always governed by the fundamental principle of adjusting cure to cause as determined by the experimental methods instituted and perfected by the great investigators, particularly those of the past century. But even when submitted to such strict experimentation, the amount of work accumulating daily is so immense, and individual ingenuity so penetrating, that the flood of facts and material becomes enormous: new agents, new aspects of the life phenomenon revealed, new concepts and interpretations. The instability of current therapeutics consists in this very displacement and substitution of new facts and resources by still newer, better, and more adequate facts and resources.

The present-day scientific research, even though based on the experimental cure-to-cause principle set forth by Claude Bernard in his classic text, tends to take on a certain "provisory" character substantially different from the work of scientists of the past century, who always tried to achieve definitive scientific conquests, unshakeably interpreted. It is really a curious fact that the improving of scientific methods and greater strictness in experimental procedure should have led to such an instability in therapeutics. Everything points to an even greater flexibility, so that the future physician will govern himself not by strict formulas, but by an eclecticism requiring ever better and more up-to-date knowledge.

Before the war of 1914–1918, a series of fundamental facts and concepts seemed to have been firmly established. There were acknowledged the growing possibilities in specific immunization, asepsis, chemical and cytological methods ap-

plied to the study of the living, anatomo-clinical methods for the interpretation of disease, and graphic and radiologic records. Chemical physiology and biological physics had largely replaced anatomy and mechanical physiology. The principal therapeutic weapons were specific serums and immunizing vaccines; some organo-therapeutic products, especially the thyroid preparations, which were one of the greatest achievements of the past century; gas anesthesia; analgesics; anti-syphilis agents, especially the organic arsenicals, so wildly and dangerously used in the beginning; antiseptics; and some of the old dependable drugs such as quinine, digitalis, and the salicylates. Nevertheless, the physician was still unarmed against many diseases: septicemia, especially pyogenic, toxic conditions of any kind, and metabolic and growth disturbances. Death rates from puerperal infection were generally more than 50%; the inevitable outcome of diabetes was coma and the death rate due to acetonuric coma was 95% or over; death-case rates in septic meningitis were 60 to 70% or higher; the old English proverb, "Once a leper always a leper" was being applied to syphilis as well; and there was both wit and truth in the statement that a famous English physician was said to treat his typhoid cases with "faith, hope, and charity."

On the other hand, many great scourges had been definitely eliminated; especially the great pestilences, and therapeutics was little by little acquiring a sense of greater security and capacity. About 1900 three great encyclopedias of therapeutics and pharmacodynamics had been published: one in French and two in German; and several congresses devoted exclusively to therapeutics were held, although more in a spirit of exhibiting prevailing therapeutic measures than in an attempt at coordination.

For this reason, certain phenomena of the 1914–1918 war appeared as a painful and grievous surprise, for which the physicians were at first wholly unprepared: the inability to combat severe hemorrhage; the terrible, immediate danger of those poisoned by gas, most of whom died of suffocation; and the violent recurrence of the old plagues of the wounded: gas gangrene, traumatic necrosis, septic edema, and wound corruption.

It happens that during great wars certain therapeutic conquests find a wider use, or are more urgently brought to practical application, so that they seem to have come into being during the war. Thus it was that during the 1914–1918 war there were achieved and put into successful use three therapeutic measures: blood transfusion, oxygen-therapy, and septic (anaerobic) antitoxins.

The circumstances leading to the widespread use of oxygen-therapy are familiar. It was undoubtedly known a long time ago; even in the days when North American surgeons and dentists were discovering the possibilities of gas anesthesia, there had existed in North America, in 1798, a "Pneumatic Institute" whose founder, Beddoes, pretended to cure all diseases by the use of gases, including oxygen. His excesses and failures discredited him. Paul Bert in 1878 and Mosso and Richet in 1880 advised unsuccessfully the installation of oxygen chambers in the hospital of Paris. But, in reality, oxygen-therapy was used inefficiently and almost always as a "last rite" for the dying. During the 1914–1918 war the first trials with oxygen in gassed persons were by subcutaneous injection and, naturally, fruitless. It was only when the English (Haldane *et al.*) and Belgian (Nolf *et al.*) physiologists advised and practiced inhalation that oxygen-therapy demonstrated its usefulness and saved many lives. There date from that time the use of Haldane's masks and Nolf's nasal tubes for inhalation, and the perfection and widespread use of oxygen-therapy.

Blood transfusion has also been known for centuries. By 1875 Landois had recorded 347 attempts at blood transfusion in man, some of them successful, such

as the first two by Denis of Montpellier in 1667, but the majority disastrous, as was Denis's last attempt, which cost him his right to practice. The three fundamental conditions governing transfusion were then unknown: perfect asepsis, inhibition of blood coagulation, and the selection of compatible types. Modern asepsis and Landsteiner's (Vienna, 1900) discovery of the iso-agglutinins in human blood, and the identification in 1902 of a fourth blood group, by De Castello and Sturll, permitting the classification of blood into four groups and the determination of their compatibility, partially solved the problem. But that of coagulation remained. The injection of simple saline solutions maintained the fluidity for only a few minutes more, since the solution filtered through the capillaries. The first attempts to treat the wounded who had lost quantities of blood, during the 1914–1918 war, were chiefly carried out by the English physiologist Bayliss, and consisted in the injection of viscous suspensions of colloids, gelatine, and acacia of only relative efficacy and not free from danger. Transfusions without anticoagulants had to be made very quickly, which did not always rid them of danger, or by artery-vein arm-to-arm anastomosis, difficult in practice. A decisive improvement was the use of anticoagulants, especially sodium citrate. Its anticoagulant action was well known to physiologists since Schmidt and Arthus (1880–1890); more recently it had been used in blood transfusion by the Belgian Hustin (1914) and the Argentine Agote (1914). After that it was systematically used in blood transfusion in man and it was already widely employed in the later years of the war.

Septic infection due to anaerobes in wounds has always caused a high death rate, especially during war with the movement of masses of men and the accumulation in field hospitals of great numbers of wounded suffering from severe traumas: ragged wounds, compound fractures, etc. The appearance of edema and of foamy and evil smelling pus are indications of extreme gravity and formerly called for amputation—the "preventive amputation" which Lister called the infamy of surgery, and which was responsible for a case-death rate of 40 to 70% in the statistics of the celebrated surgeons of the pre-antiseptic era (Billroth, Lister, *et al.*), and of 90% in those of the French Army surgeons (Larrey, Desgenettes, and Desault) in the wars of the French Revolution and of the Empire, and in those of Guthrie of the British Army at Waterloo. In peacetime surgery, with proper antisepsis and asepsis, infection caused by anaerobes was nearly always avoided, and up to a certain point septic infections in wounds were almost forgotten, or considered rare. Therefore the violent reappearance of septic wounds during 1914–1918 came as a great surprise: septic edema, gas gangrene, traumatic necrosis, and putrefaction, favored by the richly fertilized soil of France by the necessity of treating these wounds as hastily as possible. Physicians and surgeons found themselves wholly unprepared. In fact, there was reproduced during the first few months of war the terrible mortality of the wounded in the French ambulances of 1870–71 and of the Russian field hospitals in the Crimean war where the heroic Russian surgeon Pirogoff battled so ineffectually. The great therapeutic achievement of the 1914–1918 war was the identification of the majority of the anaerobic germs and in the preparation on the French front of antitoxins, by the British and North American bacteriologists Bull and Pritchett, Robertson, Bergstein, and others, and the French, such as Weinberg, Seguin, Rosenthal, and Veillon. The efficacy of these antitoxins was recognized in 1919 by the British Medical Congress.

During the uneasy interval of peace from 1919 to 1939, therapeutics took great strides forward. The drug industry reached an extraordinary development, often actually harmful because of the unnecessary multiplication of an extremely diversified, impossible-to-remember nomenclature and the likewise unnecessary

diversification presenting the same drug under a confusing variety of forms. However, this expansion also brought with it the serious and efficient analyses which many of these great industrial developments have presented to medical science. This increased activity in the drug industry and the multiplication of great government-supported scientific institutions have been the most active impulses towards the present acceleration of scientific achievements in medicine.

The principal therapeutic triumphs during this period were in the ever-increasing extension of organotherapy, especially insulin, the discovery of which began with the famous experiment of Mering and Minkowski in 1889 and which was attained after many trials by the Toronto physiologists in 1921–1922; the various ovarian preparations including estrogens and progestogens; pituitary preparations, still far from exhausted; parathyroid acid extracts; liver and stomach preparations, and the improvement of thyroid products. Insulin and liver products were especially important. But of even greater importance was the universal legislation adopted regarding all organotherapeutic products, initiated by the Congress of Edinburgh in 1923, at which the first standards for therapeutic activity were adopted, to be added to later. Progress, not only in a practical way, but also in concept, has been the possibility of achieving by chemical synthesis the production of many of these endocrine principles: androgens, estrogens, and progestogens; more significant still because in many cases synthetic preparations are more active than the matter secreted by the glands themselves. Nevertheless, endocrine principles of a protein nature, such as insulin, pituitary hormones, and parathyroids, have so far not been made synthetically, and it will probably be a long time before this is achieved.

Another therapeutic agent of great value has been made possible by the discovery of vitamins. To the ancient knowledge of the great scourges due to regional and endemic malnutrition, such as scurvy, beri-beri, pellagra, xerophthalmia, was added the discovery of the partial, sub-clinical, and associated malnutrition states, which have taken an important place in current civilian pathology. Some eight or ten vitamins have been recognized: A, B_1, B_2, B_6, PP, C, K, E, D, all important in the treatment of various disturbances. Many symptoms and sindromes which previously had been attributed to other causes are now cured or at least improved or retarded by vitamins. For example: dental caries (vitamins A, C, D); bone disorders, osteitis, rickets and osteomalacia (vitamins C and D); neuritic and psychic disturbances, algias, delirium, polyneuritis (B vitamins); hemorrhagic sindromes in both adult and child (vitamins K and C); cardiac disorders (B vitamins); gastro-intestinal disturbances, anorexia, diarrheas, constipation (B vitamins); and finally, coryzas, asthenias, and dermitis. Malnutrition pathology is becoming more and more important, partly because of the wide use of canned meats, vegetables and fruits, and the refined food products such as white flour, white bread, white sugar, and sterilized milk, which lose much of their valuable vitamin content in processing. This has led to the enriching of canned and refined foods by the addition of vitamins B, C, K, and D. When the growing possibility of chemical synthesis of many vitamins is considered, there may be visualized a tendency, which will surely not stop at vitamins, toward the synthetic preparation of food.

The improvement of many of the standard remedies of the old therapeutics, the knowledge of which appeared to be exhausted, has brought about the acquisition of better and greater resources. For example, in the case of digitalis, better knowledge of its pharmacodynamic action has permitted extension of its use and adjustment of its posology. The old single dose recommended by Potain and the French cardiologists of the latter part of the preceding century (50 drops of a

solution of chloroformic digitalin) and the restricted use in cases of tachycardia due to fibrillation, prescribed by the British Mackenzie and Lewis, have been replaced by a wider concept and better results with the use of larger doses en masse or by venous injection. Also, through the studies, mainly experimental, of cholagogues, choleretics, and cholecystokinetics, begun years ago by the Edinburgh Commission (1869) effective agents derived from bile salts have been obtained, in a way perpetuating the old idea supported by Stadelman in 1896 and Dufour and Doyen in 1897, that the best cholagogue is the bile itself, but bile improved by purification and the use of bile salts and other derivatives. Progress in diuretics has not been as considerable. The number of diuretic preparations and chemical substances proposed by various workers and industrialists has greatly increased, but for the most part their action depends on two basic factors: an increase of glomerular filtrate and a decrease of the tubular reabsorption of water. The "concentration capacity" of the kidney is little or not at all increased in pathological cases, and Bright's lament of 1836 still holds good in kidney disease.

Remedies for diseases of the nervous system have also multiplied from varied pharmacodynamic bases: hypnotics, general gaseous anesthetics of increasing harmlessness, antispasmodics which may be graduated at will, local anesthetics to substitute cocaine, and central analgesics derived from or substituting for opium which will undoubtedly displace that ancient analgesic.

Besides these depressive remedies for the nervous system, two bold agents have been introduced: those acting on the autonomic function such as the sympathetic-mimetic epinephrine substitutes and parasympathetic stimulants such as acetylcholine and physostigmine; and the convulsion therapy used in treating depressive and affective psychoses and epilepsy, in which the provocation of the discharge of the convulsion would constitute, according to some authorities, the best method of relieving psychic epilepsy and the lesser fits of petit mal, so resistant to antispasmodic drugs.

A notable example of multiple agents derived from the same drug is that of the ergot alkaloids. Since Tanret in 1875 isolated ergotinin, the first alkaloid from ergot, the number of alkaloids isolated from this fungus has increased considerably, especially since the publication of the work of Barger and Carr, Stoll and Binckhardt (1937), Smith and Timmis (1937), Dudley and Moir (1935), Thompson (1935), and many others, justifying Barger's statement that "ergot is a veritable treasure-house of pharmacological constituents." If the complex and variable composition of this fungus is compared with the equally unstable and complex composition of the digitalis leaf, the purin-rich vegetables, or of opium, it may be understood that the pharmacodynamic action of a vegetable drug cannot be referred to as a "single active unique and invariable principle." Its chemical composition is unstable and follows varying non-definitive formulas, the exact composition changing according to the time it is gathered, its preservation, cultivation, etc. This flexibility explains many discrepancies in chemical analyses. The old concept of the "active vegetable principle" started during the last century when the first quinine alkaloids were isolated by Pelletier and Caventou, and later with the isolation of those of morphine and strychnine, between 1810 and 1820, when all pharmacodynamic action was referred to a "unique and invariable vegetable principle" such as an alkaloid, or glucoside, has been modified, with the admission that within certain limits a vegetable has a very variable composition and pharmacodynamic activity. Proceeding in almost the same manner—varying slightly a fundamental synthetic chemical formula—the chemist has succeeded in synthesizing a long series of artificial substances with the same fundamental pharmacodynamic action, but from varied bases—as witness the fruitful work of

Barger and Dale, 1810, on the sympathetic-mimetic phenylamine epinephrine substitutes.

This orientation of experimental pharmacodynamics and pharmaceutical chemistry, the two great pillars upon which rests the drug industry—one of the greatest industries of the present-day world—has constantly accentuated that extraordinary mobility of applied therapeutics to which reference has already been made.

Metallotherapy is also another outstandng example of the multiplication of therapeutic means. Years ago various metals were used in treating disease: mercury, used by the Arabs in Spain, to cure itch and pediculosis in the XI century; and recommended by Berengario (de Carpi), Fracastorius, and Juan de Vigo between 1400 to 1500 against syphilis; "potable gold," lead, and antimony, used against a variety of diseases. At the beginning of the present century, however, the use of metals had been practically limited to mercury against syphilis, and that used almost entirely empirically. When, between 1905 and 1907, the antiparasitic action of arsenicals was discovered by various workers, and when Ehrlich and his coworkers, starting with atoxyl, obtained a series of organic arsenicals for the treatment of syphilis (1907–1910), it seemed that a specific parasitocidal action was involved. Ehrlich's basic aim, to which a great part of his labor was directed was precisely the securing of his famous "magic bullets," that is, substances with a great parasitotropic but non-organotropic activity, attacking the parasite only with no affinity for the body cells. On this concept he built his theory and succeeded in developing his wonderful antisyphilitic agents. At present all these ideas on specific antiparasitic chemotherapy have been shaken, and the lack of knowledge of the antiparasitic action of many other metals such as bismuth, antimony and vanadium in such diseases as spirochetosis and trypanosomiasis, has resulted in the substitution for that concept of broader, though not yet well defined ideas of bacteriostasis, the stimulation of the reticulo-endothelial system, macrophagy, extra and intracellular changes of equilibrium, local inflammatory and visceral aseptic reactions, acceleration (catalysis) of the biological defenses, and so forth, knowledge of which is still far from precise. Metallotherapy (mercury, arsenic, antimony, bismuth) constitutes at the present time one of the most efficient resources against internal parasites, though its action seems to be obtained only at the cost of local or visceral reactions which it is not always possible to regulate, and therein lies the greatest risk.

Treatment of malaria, perhaps the world's most prevalent disease, has progressed considerably. To the cinchona bark which the Countess of Cinchon, wife of the Viceroy of Peru, introduced into Spain in 1636 and which led to one of the most scandalous fraudulent speculations in medical history, have been added quinine and other alkaloids, and finally other synthetic drugs such as plasmochin, quinoplasmin, radoquin, and atebrin, which have greatly improved therapeutic action.

On the other hand, in spite of long years of use, the therapeutic efficacy of some old drugs chaulmoogra for leprosy, gold for tuberculosis, and salicylates for acute rheumatism is still debated. This uncertainty is in contrast to the demonstrated efficacy of other drugs accepted without question soon after being proposed, such as liver therapy for anemia, arsenicals for syphilis, and insulin for diabetes, and casts some doubt as to the real curative qualities of the debated group.

During the last four or five years, two great therapeutic media have been introduced and widely used: the bacteriostatic anti-infectious agents, namely sulfanilamides and penicillin; and plasmotherapy. As during the war of 1914–1918

there came the development of blood transfusion, oxygen-therapy, and anti-anaerobic serum therapy, so it may be said that in this last war the sulfanilamides, penicillin and plasmotherapy came into their own. The history of these three marvelous developments is too recent and too well-known to need repetition, but mention may be made of the different manner in which the sulfas and penicillin came into practical use. The discovery of the anti-infectious action of the azoic sulfanilamides was achieved in a non-official industrial institution (the Bayer laboratories) by one of the laboratory experts, and the product was immediately placed at the disposal of the public without restrictions. There ensued the manufacture of similar drugs by other companies, commercial competition, the multiplicity of the chemical variants and the great diversification in nomenclature which was further increased by the local preparations in each country. All this caused great confusion which still exists.

On the other hand, penicillin was developed in official institutions and not only its production, but also its industrialization, sale, and even its application were kept under strict control, avoiding most of the confusion that surrounded the sulfanilamides.

A therapeutic agent already well known, but which seems one of the most important of the present day and which has recently seen more precise and wider use, is carbon dioxide by inhalation. It is one of the most powerful stimulants, mainly of pulmonary ventilation and of broncho-pulmonary reflexes, an expectorant, and a remedy against apnea (post-anesthesic, of the new-born, post-operative, etc.). It is undoubtedly a very valuable tool which every physician should learn to handle. With oxygen therapy and the general gaseous anesthetics, it completes this increasingly important group, the preparation of which ought to be controlled and encouraged by the government of every country and which should be made available to every patient needing them.

During these last thirty years since the beginning of the war of 1914–1918, the number of new and perfected drugs has been constantly increasing and will continue to increase, making it difficult for the practising physician to keep up to date. The adoption of universal legislation for the adequate control of such vast material and the dissemination of information by the most rapid means and to all physicians becomes more and more necessary. Medicine in general and therapeutics even more so, need increasingly greater governmental supervision and control or some sort of universal regulation.

Pneumonite bovídea no Brasil.—Octavio de Magalhães, (*S. Paulo Méd.*, 460, dbro. 1944) expõe o histórico da pneumoenterite dos bezerros ou melhor dos bovídeos no Brasil. Diz que desde 1919, quando assistiu a panzootia em Minas Gerais, onde morreram cêrca de 60,000 bovídeos, havia demonstrado pela primeira vez que o agente etiológico da moléstia era um virus filtrável, e que tinha a propriedade, quando inoculado nos bezerros sadios, de provocar além dos polmões e numerosas outras complicações, pneumonias e enterites. Descreveu também pela primeira vez as diferentes formas clínicas da moléstia: super aguda ou fulminante; aguda; crônica (cutânea, intestinal e tôxica); e anômalas. Às vêzes, no quadro clínico dominam os sintomas pulmonares, noutros os intestinais. Conseguiu, desde 1928, uma vacina preventiva com o virus contra pneumoenterite dos bezerros e cujos resultados práticados nos campos em Minas Gerais, durante 8 anos, com 110,427 doses, foram realmente bons (95 a 100% de imunização). Empregou desde agôsto de 1942, a quimioterapia pelos sulfanilamidas na terapêutica curativa da moléstia, também com ótimos resultados.