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Editorial

"CONTINUING MEDICAL EDUCATION"

This issue provides a good entry into this subject. In it are included papers which were presented at the Dalhousie Post-Graduate "Week in Medicine" last March.

The "why" of post-graduate study needs no explanation—it is the "how" that is our present concern. If we think of learning as a spectrum, it will range between extremes of passivitiy and activity. The reader of this article is the passive learner while the writer is the active one. The student who attended the Week in Medicine is in between, though much closer to the active end.

It doesn't take a G.P. very long to learn, after attempts at study have ended in slumber, that the passive approach is the ultimate in futility. So he decides that the only way is to take off on one of the several Post-Graduate "Weeks" sponsored by Dalhousie University. After a week in his chosen topic he returns to his practice up-to-date and reorientated. He is able to look the pharmaceutical house representative right in the eye again but, more important, he is able to give his patients better care.

He has not been a passive learner, but compared with those who took part in giving the course, he has not been very active. The writer attended the "Week in Medicine" from which the bulk of this issue comes and concluded that the ratio of givers to receivers was about four to one. From this point of view of learning, it was these givers who were the optimum receivers. Without denying this, our average G.P. may feel himself excluded from this group. He needn't. All he needs is a subject—and everyone has his most interesting case. With interest as his stimulus, time and drooping lids will not longer be a problem. In the research for the article when his own resources are exhausted, the Medical-Dental Library at Dalhousie can fill the gaps. A letter to the Librarian, stating the requirements, will be answered with all the references and the appropriate texts and periodicals on a two-week loan basis. Anything not available then can be borrowed by the Library from one of the British or American reference libraries.

And if he cannot get his paper published? (Highly unlikely, as long as this article-hungry Nova Scotia Medical Bulletin exists.) He is not the loser even then, because he has become an optimum receiver, away out at the active learner end of the study spectrum.

J. L. F.

Nova Scotia Day At The C. M. A. Meeting

A Luncheon Address by
The Honorable R. L. Stanfield, Premier of Nova Scotia
June 17th, 1958

I welcome you to a part of Canada which has had a very long history, as time is measured on this continent. I welcome you to a part of Canada which in the earliest days saw and participated in the ebb and flow of war, which was to determine the ultimate destiny of this nation.

This is the oldest part of Canada, for since the year 1605 there has been continuous white settlement in Nova Scotia. No part of Canada—no part of the United States, with the exception of the ancient Spanish settlements in Florida—can boast of so ancient a civilizaton.

You will find here a Province peopled by four great races—French, English, Scottish and Irish—with a strong sprinkling of Dutch and German in the County of Lunenburg.

The French are the descendants of the Acadians who, exiled from this Province in 1755, found their way back, through trackless forests, treacherous rivers and stormy seas, to the land which had been their home for one hundred years.

The English are the descendants of the early pioneers who founded the first English settlements in Nova Scotia, and of those who came here from the United States before the American War of Independence and of over 20,000 Loyalists who found refuge in this Province after that war.

The Scots and the Irish, bringing with them their first love of freedom and independence, found a home in this new land, and have made their imprint on the culture of this Province.

This is the land where Sir William Alexander, a great pioneer with a prophet's faith, a promoter, a gentleman adventurer with the courage of his ancient race, hoped to build a New Scotland in America. He was given by Royal Charter in the year 1621 a Grant of Land which may be described approximately as the present-day Nova Scotia, New Brunswick, part of the State of Maine, and part of the Province of Quebec.

Through the years there have been changes in the territorial boundaries of this Province. In 1763 Prince Edward Island was annexed to Nova Scotia, and in 1769 it became a separate colony. In 1784 the territory which is now the Province of New Brunswick was separated from Nova Scotia and became a separate colony. The island of Cape Breton was annexed to Nova Scotia in 1763, became a separate colony in 1784, and was annexed to Nova Scotia again in 1820.

The year 1958 marks not only the Three Hundred and Fiftieth Anniversary of the founding of Quebec;—which occurred three years after the building of the Habitation at Port Royal—but also such significant events as the One Hundredth Anniversary of the transfer to the Province of control over the mines in Nova Scotia—the Two Hundredth Anniversary of the second capture of Louisburg—and the Two Hundredth Anniversary of the establishment of the first Canadian House of Assembly.

Today we virtually take our governmental system for granted. But when two centuries ago the elected representatives of the people of this Province first met in the old Court House, at the corner of Buckingham and Argyle

Streets, the foundation of government by consent was laid. This was a major milestone in our constitutional evolution—a development that was eventually to lead on to Responsible Government, Confederation, and the Statute of Westminster.

Why was the House of Assembly of Nova Scotia established two hundred years ago? Generally, in times of crisis and struggle, the liberties of citizens are curtailed rather than enlarged. Yet it was in the year 1758, in the midst of the Seven Years' War, (one of the most decisive conflicts in the annals of mankind) that this seed of English liberty was planted here, and the people of Nova Scotia through their elected representatives began toshare in government. That is one significant factor. It makes a longer look at the circumstances even more necessary.

After changing hands nine or ten times, Acadia, or Nova Scotia, ultimately became British by the final capture of Port Royal in 1710, and by the Treaty of Utrecht in 1713.

At that time however France retained both Cape Breton Island and Prince Edward Island. And soon strove to squeeze the old Acadia, which had been ceded to the British, into the peninsular part of the Province. Nova Scotia was thus confronted with external danger.

Internally, it had problems too. With fewer than a dozen families of English origin at Annapolis Royal and a number of fishermen frequenting Canso during the fishing season, the Acadians formed the bulk of the population Because of their racial and religious background, they constituted a new problem for English administrators of those days.

Eventually, in 1749, Halifax was founded at the expense of the British Government, as a counterpoise to Louisburg, and at last a real effort was made to place settlers of British origin in this Province. Approximately 2700 settlers crossed the Atlantic from the Old Country, to Halifax, in that year, and soon a considerable number of New Englanderx hastened to this new town, to take advantage of opportunities in trade or to claim privileges accorded to settlers.

Within the next few years more than 2500 "foreign Protestants," as they were called, from the continent of Europe congregated here. They had been promised farms in Nova Scotia, but on account of the French and Indian menace had to be maintained in the town of Halifax until many of them became founders of Lunenburg in 1753.

Until security and representative governmental institutions were provided, few New England farmers or fishermen would settle in the Province. But with the onset of hostilities, in 1755, including the capture of Beausejour and Braddock's defeat, and with the official outbreak of the Seven Years' War, in 1756, new developments took place.

Louisburg was captured for the second time in 1758, thereby depriving the Indian allies of the French of support from that quarter. With the capture of Quebec and Montreal within the next two years the French and Indian threat to Nova Scotia was virtually removed. Thus one major obstacle to New England immigration had been erased.

Meantime the other important impediment had also been eradicated. Governor Cornwallis, the founder of Halifax, had been directed to summon an Assembly as soon as it was expedient to do so—but representatives were to be elected by freeholders in each township, and for the time being the population of qualified electors was too limited for Writs to be issued. The Governor was

thereupon reminded that when the population expanded he must not forget his instructions.

Hopson, his successor, was instructed to call an Assembly, when the townships (apparently including at least one other than Halifax) had fifty or more families settled in each of them. Qualified electors might be found at Halifax, but not for the present at Lunenburg, whose inhabitants being mostly foreigners must first have seven years' residence in Nova Scotia. By the time Lawrence succeeded Hopson, the order had become merely the recognition of a possibility—in case it should be found necessary.

Two factors provided the final impulse. One was that the Board of Trade in London doubted the legal propriety of legislation by Governor and Council—when the Governor's Commission and Instructions both took it for granted that the only possible way of making laws was with the assent of an Assembly. When the Law Officers of the Crown in England gave it as their opinion, that the Governor and Council alone were not authorized to make laws, action became imperative. The other factor was the determination of the American agitators in Halifax—who exaggerated grievances—complained about placemen, and demanded the establishment of a House of Assembly.

As a Governor of a barrier colony in time of war, and being himself directly involved in the siege of Louisburg in that year, Governor Lawrence might consider such a change very inexpedient at that time. Yet, upon positive orders from England, he took the necessary steps which resulted in the convening of the first House of Assembly, on October 2, 1758.

Thus it was that this Province owed its House of Assembly to the exercise of the royal prerogative. On the other hand, Upper and Lower Canada were later each to establish their House of Assembly, not by this means, but by the sanction of Imperial Statute—The Constitutional Act of 1791.

What was the significance of the establishment of the first Canadian House of Assembly—the House of Assembly of Nova Scotia—in 1758? There were at least two **immediate** results. First of all, Representative Government was begun—elected representatives of the people could now for the first time share in making laws for the Province. Secondly, it paved the way for an inflow of new settlers. If New Englanders had been averse to migrating to Nova Scotia while it was insecure and lacking in representative governmental institutions, they were very ready to come in substantial numbers once those impediments were removed.

As a result, between 1760 and 1768, New England planters and fishermen poured into the Province, to the number of about eight thousand, in a substantial pre-Loyalist migration, which laid abiding foundations, particularly in the western part of the Province.

Even though Representative Government was conceded in 1758, this did not provide democratic government in the way we know it. There was then neither party government nor responsible government. Members of the Executive Council were then not chosen from the House of Assembly. They were nominated by the Governor, and went on, if not forever, generally for life. They were not accountable to the elected representatives of the people. Nor did they need to resign if they did not possess the confidence of the House of Assembly.

There were institutions of Representative Government in certain other colonies, such as Virginia, Bermuda, and Massachusetts, prior to 1758, but the House of Assembly of Nova Scotia of that year was the first to be established

in any part of what is now Canada. Once it was set up, Responsible Government was bound to come, as come it did in 1848. It was the initial indispensable milestone in a series of significant stages in Canadian constitutional development.

Lest I leave you with the impression that the people of Nova Scotia were only concerned with war, rumours of war, and the making of a constitution, let me hasten to assure you that such was not the case.

Halifax was a garrison city and a naval establishment. The leading civil authorities, the military and the naval personnel formed a lively society, and the entertainments of those days were resplendent with the colourful uniforms of the day.

What went on within the select circle that surrounded the Governor was never a matter for public report, although it may well have been the subject of general gossip and speculation. Were it not for certain private papers that have survived, we should be mostly in the dark as to the social life in Halifax in the earlier days.

I would like to quote one or two excerpts from the diary of William Dyott —"In the evening a ball at the Governor's, we went about seven; His Royal Highness, Prince William Henry, came about half later, and almost immediately began country dances—we changed partners every dance; he danced with all the pretty women in the room and was just as affable as any other man."

And, again in reporting on a ball that was given on Prince Henry's ship, which was then lying in the Harbour, he wrote: "The company assembled at seven o'clock. There were 14 ladies and 30 gentlemen. We danced till one o'clock. Upwards of sixty people sat down to supper at a table almost in the form of a horse shoe. We remained more than an hour at supper. We danced till three o'clock, when the champagne began to operate with some of the gentlemen, and the ladies thought it near time to go on shore. I never spent a more joyous night."

In conclusion, may I say that it has been a pleasure and a privilege to be here with you today. I hope that you are having a useful and pleasant conference and that you will take away with you many happy memories of your visit to Nova Scotia.

The Prophylaxis of Rheumatic Fever

John B. Armstrong, M.D., F.R.C.P. (C.)
Medical Director, National Heart Foundation of Canada.

ALTHOUGH Rheumatic Fever may have been seen by the ancient Greeks, it was not differentiated from other forms of rheumatism until the mid-17th century. Sydenham gave an early description of the disease, but its name is attributed to Haygarth who, in 1805, wrote a clinical monograph on Rheumatic Fever. By the mid-19th century, it was recognized as a separate entity and that it might be infectious. Though some relationship to heart disease had been suggested, indeed, Bouillard, in 1840, had emphasized the great frequency of endocarditis and pericarditis, it was not until 1904 that Aschoff's detailed description of the myocardial lesions bearing his name was published. With a more precise concept of the disease, the "focus of infection," and particularly tonsilitis, became quite popular as an etiological factor, and out of this phase, about 1930, the incrimination of the Group A haemolytic streptococcus followed. As perhaps 3% of persons with the appropriate streptococcal infections develop Rheumatic Fever, much is yet to be learned about the mechanism by which the specific tissue reactions are incurred, However, it is clear that heredity as well as environmental factors are involved. and the latter are both sociological and climatological. Thus, from a morass of joint disorders, there gradually arose a disease that may be defined as inflammatory, with protean manifestations commonly affecting the joints but of particular significance for its involvement of the heart.

In view of the confusing nature of Rheumatic Fever, we are indebted to the late Dr. T. Duckett Jones for outlining diagnostic criteria for this illness. These criteria, later modified (1), have been divided into major and minor categories. The five Major Diagnostic Criteria are:

(1) Carditis—accepting any one of the following:

  (a) Murmurs, one or more of
  —significant apical systolic (70)—
  filling systole and without change with position or respiration;
  —apical mid-diastolic (35) —
  low-pitched and short, heard best in the left lateral position;
  —basal diastolic (35) —
  early, short and diminuendo, heard best along the left sternal border;

  (b) Increasing cardiac enlargement (15) —
  obvious by X-ray;

  (c) Pericarditis (5) —
  friction rub or effusion;

  (d) Congestive failure (10) —
  in absence of other causes;

(2) Polyarthritis (45) —
migratory, with pain and limitation or redness and swelling of two or more joints;

(3) Chorea (10) —
the characteristic involuntary, quick, elaborate, irregular and varied movement;

(4) Subcutaneous nodules (15) —
shot-like bodies over extensor surfaces;

(5) Erythema marginatum (5) —
a recurrent pink rash of the trunk primarily showing a thin red margin in rings, crescents or irregular forms outlining normal skin;

The six Minor Diagnostic Criteria are:

(1) Fever (50) —

(2) Arthralgia —
joint pain without other signs of joint involvement (only when polyarthritis is not present);

(3) Prolonged P-R (35) —
only when carditis not specified;

(4) Increased ESR (90), C-reactive protein or leukococytosis—elevation of one or more of these non-specific tests, they must nlt be considered as a major criterion;

(5) Evidence of preceding beta haemolytic streptococcal infection;

(6) History of previous Rheumatic Fever or present rheumatic heart disease (25).

The diagnosis is based on *any two Major* Criteria or *one Major and two Minor* Criteria. The weakest combination is polyarthritis with fever and elevated sediemntation rate. This combination may occur in many illnesses, such as rheumatoid or gonococcal arthritis, disseminated lupus erythematosis, serum sickness, undulant fever and so forth.

The figures in parenthesis are the approximate percentage frequency of these Criteria found in the 497 patients in the U.K., U.S. joint report on a treatment trial to age 15 studied with ACTH, Cortisone and Aspirin (2).

The incidence of Rheumatic Fever is very difficult to judge. There have been reports by autopsy studies and hospital admission rates, but these are automatically selective. In the joint study mentioned above, there were six deaths in the first year, or roughly a 1% mortality. In some areas, it is a reportable illness but without firm criteria, many errors or omissions may be involved, depending on the enthusiasm of the reporting physicians. In Canada, the Province of Saskatchewan has made Rheumatic Fever a reportable illness, where it is found to occur in 0.1% of the population. As this is primarily a rural population, living in a relatively dry climate, the incidence may be higher in other areas. However, on the basis of 0.1%, Canada has 17,000 patients with acute Rheumatic Fever a year, and is producing in the order of 8,500 persons with rheumatic heart disease each year.

An unfortunate characteristic of this illness is its tendency to recur, and each recurrence increases the likelihood of permanent damage to the heart. The figures on recurrence rates vary, but, in broad terms, may be represented as follows (3);

Percent Recurrence without special therapy	Years followed	Percent Recurrence observed in strep infections treated with antibiotics
75	0- 5	6
50	6-10	4
30	11-15	2
5	16	

This table shows the marked decrease in recurrence rate with the use of antibiotics, and from such data accumulated from carefully conducted studies, it is abundantly clear that recurrences of Rheumatic Fever can be almost completely prevented. The prevention schedule varies, but that recommended by the American Heart Association, in order of preference, is:

(1) intramuscular—benzathine penicillin G—1,200,000 units—once a month;

(2) oral—sulphadiazine—0.5 to 1.0 gm.—once daily;

(3) oral—penicillin—200,000 to 250,000 units—daily.

Both drugs may produce toxic reactions—with penicillin, uticaria—and with the sulphas, skin eruptions or leukopenia. Fortunately, they tend to be rare.

The prophylactic programme should be initiated as soon as the diagnosis is made, and should be continued as long as there is appreciable risk—in other words, for at least 15 years. But such prophylaxis may present hardships to those most likely to suffer with the disease, and these same people are perhaps the least likely to continue such therapy without supervision.

In Manitoba, the drugs are made available to the medically indigent through the Department of Public Health. In Saskatchewan, a province-wide case registry has been set up and the drugs are made available to all persons, regardless of means, through regular follow-up visits of the Public Health Nurses. With the advent of Hospital Insurance in many of the other provinces, a follow-up with the supplying of the prophylactic drugs becomes a possibility through the out-patient departments. Whatever the arrangement, the bulk purchase of these drugs is not only more economic, but an organized prophylactic programme would reduce the incidence of rheumatic heart disease to negligible levels, and allay much of the illness and premature death so caused. An integrated programme for the prophylactic treatment of Rheumatic Fever in children cannot be recommended too highly.

REFERENCES

1. The Epidemiology of Rheumatic Fever—3rd Edition American Heart Association, New York, 1957.
2. Circulation 11, 343, 1955.
3. Circulation 14, 1144, 1956.

Fundamental Principles In The Clinical Use Of Antibiotics And Chemotherapeutic Agents*

G. D. Denton, M.D.

EVEN to this day it is a fact that some form of infectious disease, whether it is primary or secondary to other conditions, old or new, recognizable or obscure, diagnosed or etiologically disregarded, accounts for well over fifty percent of illnesses presented to the physician for treatment and the hope of a complete cure. With the general abundance of scientific literature filling the medical journals, together with sensational newspaper, radio and television education with respect to newer drugs, two conditions often arise. First of all the patient presents himself almost demanding, and certainly in large measure expecting a quick cure in the light of his false knowledge that infectious diseases are rapidly becoming extinct; and, secondly, the physician may often find himself assuming an unchallenged attitude towards infectious disease due in some measure to the frequent reassurance by the polite, generous yet effervescent envoy of the pharmaceutical house that another new medicine has been discovered that will quite readily handle most infections, particularly those that have not been controlled or eradicated by its lesser talented relatives. This deliberately places considerable pressure on the physician which so frequently is, at least, temporarily alleviated by the prescription for the current 'best seller' broad spectrum antibiotic.

With the widespread utilization of such readily available medications, the most pronounced effect of this seemingly benign prescription may well fit into one of the following categories:

(1) It may specifically eradicate the infectious agent from the body or retard the progress of the infection to a degree that will allow the natural body defence mechanisms to do the job.

(2) It may do essentially nothing therapeutically.

(3) It may, as we shall see later, be definitely harmful to the welfare of the patient.

If it were possible to calculate the therapeutic effect in each instance where an antibiotic is administered, both specifically and otherwise, I wonder how few cases would fall into the first category, and how many would belong in the other two. This I believe is a situation that can very definitely be considered a matter of concern, the implications of which have been entertained lightly to date, but the full force of which may have as yet not been felt.

It has been said the treatment of infectious diseases has been completely changed over the past two rather fleeting decades by something better than the Samian Clay of the once celebrated Galen, who, in praise of his favorite remedy said: "All who take this remedy recover in a short time, except those whom it doesn't help, who all die and have no relief from any other medicine. Therefore it is obvious that it fails only in incurable cases."[1] Galen's teachings have been denounced long ago but now we, having the tremendous gift of antibiotics, which have in some measure eclipsed the sulfonamides, and do

*Presented before the Atlantic Branch Canadian Public Health Association, Kentville, Nov. 1957 and the week in Medicine, March, 1958.

effect wonderful cures in several strictly limited kinds of infections, at times could ask ourselves when we prescribe these medicines if we, too, are in some respects practising the teachings of the great Galen of some eighteen centuries ago. It is with this thought that I propose to spend a few minutes in reminding ourselves of the fundamental principles to which we must adhere in the proper treatment of disease with the chemotherapeutic agents presently available.

By way of introduction it would seem fitting to quote the first paragraph from an article that appeared in the Canadian Medical Association Journal in 1946 by the late Dean of Medicine and professor of Bacteriology at McGill University, Dr. Frederick Smith: "It is not surprising, perhaps, that the microbes producing the known antibiotic substances are soil bacteria, or that the intensive search for new antibiotics centers largely in the soil. It has been recognized since the early days of bacteriology that enormous numbers of animal pathogens which return to the earth's surface do not usually survive very long and that their destruction is brought about by the normal soil bacteria. This is shown by the fact that many pathogens grow readily in sterilized soil but will not live very long in fresh soil. Historically the first antibiotic substance recognized as such was 'pyocyanase,'[2] produced by the organism of 'blue pus.' This was described in 1899. From the standpoint of therapeutics the subject began in 1929 with the discovery of penicillin."[3,4,5]

However, before discussing antibiotics let us attempt to clear up the confusion which sometimes exists in the use of various terms.[6] Protoplasmic proteins and/or lipids within the cell or forming the surface membrane may undergo alterations in the form of chemical changes or physical-chemical changes which lead to the quick death of the cell, often by protein coagulation, hydrolytic changes or membrane disintegration. This type of action represents that of a disinfectant, antiseptic or bactericidal agent and tends to take place in many types of living cells, tissue as well as bacterial. Active chemical components of living cells such as nucleic acids and nucleoproteins and enzyme systems can be interrupted in their normal activity by chemical agents specifically competing for or altering essential active radicals. When this occurs bacterial cells cannot grow, reproduce or metabolize actively and may die gradually or become weakened. Chemotherapeutic and antibiotic agents have this general mode of action. Agents that can be used to control infections are selected because they act upon chemical radicals or enzyme systems in bacteria which are not shared to any important degree by the host tissues. When dealing with rickettsia or viruses the balance is much more delicate because these are primarily living in body cells and using body cell enzyme systems and food material. Therefore agents which interfere with viruses are very likely to interfere with body cells too. It has been only quite recently that at least two antibiotics have been found which interfere particularly with rickettsia without affecting the host cells. This represents an extreme example of specificity. Some antiseptics can be used in strengths which only kill bacteria and the killing process may be slow. Some antibiotics and chemotherapeutic agents if used in optimal concentrations will kill bacteria relatively quickly. In this respect there is an overlapping in terms usually covered by the expression bacteriacidal action. Lastly there is the distinction between chemotherapeutic agents and antibiotics. Chemotherapeutic agents may be dyes like gentian violet affecting acidic groupings of nucleoproteins, may be arsenicals competing for sulphydryl groups in enzyme systems, acriflavine competing with active radicals in nucleic acids, sulfonamides blocking

the use of para-amino-benzoic acid or pyridines and thiazoles interferring with respirations through blocking the use of nicotinamide and co-enzyme one.[6]

The term antibiotic has come to be used for the group of substances isolated from living bacteria or fungi and actinomycetes, although the term really only means 'against life.' The term "antibiosis"[7] probably was used first in 1889 by Vuillemin to describe what we consider to be the survival of the fittest, whereby a creature destroys the life of another to preserve its own. The use of the word antibiosis to describe microbial antagonism was adopted by Marshall Ward[7a] ten years later. It was not, however, until 1942 that Waksman[7b] proposed the use of the term antibiotic to define those chemical substances of microbial origin that possess antimicrobial activity.

It was first thought that the mechanism of action of antibiotics differed fundamentally from that of the sulfonamides, but Goldstein,[7c] in a very thorough review of antibiotic chemotherapy marshalled evidence indicating that their actions may be substantially the same. It is, therefore, difficult to know just where to draw the line between a chemotherapeutic agent and an antibiotic, since today both can be obtained in chemically pure form. Indeed both terms are being widely used interchangeably. Although, as I have said, some of these therapeutic agents do, in some measure, combat the diseases of rickettsial and virus etiology, as yet none have shown any direct therapeutic value against toxins although these may be elaborated by organisms that are quite within the spectrum of sensitivity. This is an extremely important and frequently overlooked fact and is particularly applicable in dealing with the organisms of diphtheria, tetanus and gas gangrene.

If a particular organism fails to possess, does not require or is capable of and does replace the metabolic reaction or enzyme system upon which a certain antibiotic exerts its interference, then the organism is said to be or become resistant. This phenomenon depends perhaps more upon the therapeutic agent than the organism and is exemplified especially by streptomycin. Another factor of interest is that with antibiotics, particularly streptomycin, such a degree of resistance may develop that two types of variants are observed; one which can grow in the presence of the antibiotic and the other which grows only when the antibiotic is present. This drug dependency has been described by numerous investigators. The phenomenon of resistance merits some elaboration here as it is of paramount importance in the clinical use of antibiotics. The development of resistance like the chemotherapeutic action itself is quite independent of the host. One must remember that it is not the patient but the organism that under certain conditions becomes refractory to further chemotherapy. Resistance is encountered in two distinct forms. On the one hand a variety of bacterial species are relatively insensitive to the action of any one drug or even among sensitive species more or less resistant strains are found.[8 9] On the other hand resistant forms may arise de novo during contact of organism with drugs. That this resistance arises through spontaneous mutation during the period of contact has been well demonstrated by the work of Demerec in 1948.[10] His experiments have shown that development of high resistance follows a definite pattern which appears to be characteristic of each antibiotic and which is not determined by the bacteria involved. Resistance, he feels, arises in step-wise fashion. Two patterns of resistance were established—the penicillin pattern and the streptomycin pattern. A stepwise development of resistance is common to both but they differ significantly in the manner in which high level resistance is arrived at. In the case of

penicillin the first step resistant mutants are very uniform in their degree of resistance which is only slightly higher than that of the original strain. The streptomycin pattern of resistance differs from the penicillin pattern in that the variation between first step mutants is very great. Thus, although higher resistance may be attained in successive steps as with penicillin it may also arise in a first step mutant in the case of streptomycin. From the clinical standpoint the resistance problem offers the greatest drawback to the use of streptomycin. This emphasizes the importance of frequently determining organism sensitivity and in so far as possible increasing dosage to meet new thresholds. There is no sure method of avoiding drug fastness and particularly with streptomycin the only counter measure is to strike hard and strike fast.

Further General Considerations

1. *Toxicity.* This is, in a broad sense, manifested in two forms. One bears a definite relation to dosage; the other falls into the category of sensitivity phenomena whose incidence and severity do not depend entirely on the amount of drug administered. Either type may appear after brief or prolonged exposure to the drug. (In this respect the use of the enzyme Penicillinase for penicillin reactions has been advocated: 5,000 units, single injection, inactivates 100,000 units of penicillin).

2. *Drug levels and their maintenance.* A wholly negative attitude towards plasma levels does not seem justified despite the fact that in most cases where an antibiotic is indicated the recommended dosage schedule was formulated to produce the optimum plasma level of the antibiotic in order to exert its maximum effect. However the dangers of inadequate levels should not be overlooked in the search for the dose that will just exactly cure. Unless the immediate environment of the pathogenic organisms can be sampled as in urinary tract infections, the plasma levels remain the only indication of the probable drug concentration to which they are exposed. In the treatment of sub-acute bacterial endocarditis especially, the importance of prolonged high and constantly maintained plasma levels is stressed by Loewe and Priest. With regard to the establishment and maintenance of blood levels, little need be said here, as most people are familiar with the methods available. Suffice it is to say that this depends on the following factors: dosage; frequency of administration; rate of absorption from the drug depot; rate of drug inactivation, if any, within the body; extent of binding to plasma and other tissue proteins and rate of excretion. As you are all familiar with the various repository products, these will not be discussed in detail. It should be clear, however, that in the case of penicillin the repository method will be satisfactory for the treatment of infections requiring relatively low penicillin levels; but, in grave infections requiring a high penicillin level, intermittent aqueous injections or continuous intramuscular or intravenous infusion is the only reliable method.

3. *Synergism and Antagonism.* Sweeping generalizations with regard to combined antibiotic therapy are sometimes made, on the basis that favorable additive results have been established when two or more antibiotics and bacteriacidal agents are combined or administered together. Most of these statements are based on pure assumption; and as the literature on antibiotic research expands more and more, bits of evidence are accumulating to suggest that any combination of two antibiotics may not be synergistic but even

antagonistic, thus diminishing therapeutic efficacy. Only a short time ago, Jawetz, in reporting at the antibiotic symposium in Washington, D.C., held that synergism in antibiotics is rare. He also stated that fixed combinations of antibiotics carry a pleasant emotional appeal but have more disadvantages than merits. It was only a few years ago that he also reported a degree of antagonism between penicillin and chloromycetin.[11] Also during September of last year Jones and Finland[12] reported the results of their investigations with combinations of erythromycin, oleandomycin, spiramycin (all of which have the same antibacterial spectrum of penicillin) and tetracycline, against gram positive cocci. They found in particular that none of the combinations tested was superior to the better of the two agents. Erythromycin alone was found to be clearly superior to oleandomycin alone, and much more active than spiramycin alone; and concluded that oleandomycin and spiramycin are sufficiently inferior to erythromycin to indicate that their adoption for general use in the treatment of infections is unwarranted and should be discouraged. Other clinical reports indicate that combined therapy with penicillin and streptomycin exhibits a synergistic effect against certain staphylococcal and streptococcal infections and is often successful in curing bacterial endocarditis which ordinarily fails to respond to either drug alone, even when it has been administered in high dosage over a long period. In planning such combination therapy two groups of such antibiotics should be recognized; Group 1 includes penicillin, streptomycin, bacitracin, and neomycin. Group 2 includes tetracyclines, chloramphenicol, erythromycin and novobiocin. Combinations of drugs from group 1 may be synergistic: effects from two or more drugs from group 2 are simply additive.[13] If an antibiotic is selected from each group synergism or antagonism may occur: thus combinations of this type must be tested against the bacterial strain in vitro before therapeutic use.[13]

It might be well to stress here that when combined therapy is used for serious infections, the infectious agents should be hit hard at once with the proposed combination of therapeutic agents, rather than using the agents in succession as is so often done.

Now that we have covered some of the basic fundamentals let us turn to the practical considerations that meet us in the practice of therapeutic medicine.

a. *The patient.* The physician and nurse must not forget that patients and not their microbes are treated. Drugs only suppress the growth of infectious agents until the body can develop its own defences. Antibiotics that would heal tuberculous cavities and amoebic ulcerations cannot be imagined. The maintenance of nutrition and hydration, the security of anatomical and physical rest, attention to excretion and provision of good nursing care are still essential to good medication. The age of the patient other than the determination of dosage of the therapeutic agent to be used is of little significance. It is important, however, to ascertain whether the patient has a history of previous therapy, the agent used, the amount and the duration of treatment.

Increasing recognition of sensitivity reaction is an established fact, and if a severe reaction occurs it at least is not beneficial and may be deleterious. Such reactions are commonly skin eruptions or some form of angioneurotic oedema, both of which can be extremely disabling. Then it is well to keep in mind the serum sickness type of reaction following the administration of particularly penicillin and aureomycin. This is particularly important in pediatrics because penicillin is often given for

pharyngitis. The later appearance of joint pain and swelling has been confusing in the differential diagnosis of rheumatic fever and has caused needless treatment of children for this disease. Intramuscular benzathine penicillin has been shown to cause the appearance of C-reactive protein in the blood, elevation of the erythrocyte sedimentation rate and fever. This must be differentiated from rheumatic activity and rheumatic rebounds.[14]

b. *Environment.* Whether the patient is to be treated in the home or in the hospital is also of great importance. With what ease can the therapeutic agent be given? What will the cost of the antibiotic or the auxilliary cost of its administration be to the patient? These questions should enter into the physician's calculations. If two agents are equally effective against a given infectious process, then the one which will bring about the betterment at the lowest cost to the patient should be used. This does not necessarily mean the cheapest antibiotic which can be given with least auxilliary charges, such as those of hospitalization and frequent visits of patient or physician. Thus a more expensive antibiotic which can be given safely and effectively by mouth in the home might be the choice rather than a cheaper one that requires hospitalization or the physician's frequent attendance for its administration. If the patient is in hospital, the physician should and must maintain close co-operation with the bacteriological laboratory to be informed about the nature of the causative agent, its susceptibility to an ever increasing long series of antibiotics, and in some cases the blood levels achieved if indicated by the medication. It is no exaggeration to say that when treating a severe illness with antibiotics the laboratory is as much in attendance as the physician and nurse, and therefore should be treated as such.

c. *Disease.* A correct diagnosis first of all is convenient! If this has been established, then one knows if the etiological agent is a bacterium, spirochete, virus, rickettsia, parasite or unknown. If the diagnosis is not known, there is usually time to make one before attacking the patient with antibiotics, or else one is faced with the question—must I use a combination of chemotherapy as more or less a last measure? Not only is the diagnosis important, but to know the natural course of the disease is essential, in many cases, in order to assess therapeutic response. In the recent literature, the following statement can be seen: "Obviously chemotherapeutic agents effect their results by a specific action on the invading organism irrespective of the form which the disease may assume." This is not entirely true. The form is important.

Is the disease acute, sub-acute or chronic? In many cases this fact regulates dosage and duration of administration. Is the infection localized? or systemic? Are there any factors present that will interfere with the action of the antibiotic such as pus, necrotic tissue, mucus or some neutralizing agent? Will the antibiotic get to where I want it to go, and in sufficient concentration? It is well to remember that, aside from local administration which at times is an important adjunct, the diffusibility of an antibiotic is directly dependent on the blood supply. Thus the prostate, for example, is a relatively avascular tissue, and consequently might explain the chronicity of prostatitis despite what seemed to be adequate therapy. Eagle[15] has shown that concentrations of peni-

cillin in plasma must be kept up to ten times that required to inhibit susceptible organism in an avascular site. The presence of fibrosis, which is often met with in chronic diseases, must be taken into consideration. An antibiotic must reach the organisms in a solution in order to act. An other point to remember is that, in some cases following intramuscular or intravenous or oral administration of average dosage, most antibiotics diffuse reasonably well into amniotic fluid and placental blood, intraoccular fluid and peritoneal cavity. But, with some exceptions, there is virtually no absorption into cerebrospinal fluid, pleural cavity or prostatic fluid unless massive doses are used. This is particularly true of streptomycin and terramycin. Thus, mode of administration of the antibiotic depends in many instances on the disease itself. Furthermore, the realization of any concomitant measures such as surgical drainage or removal, if indicated, to enable or enhance the activity of the therapeutic agent is imperative. Antibiotics will not replace surgery where the latter is indicated.

In the treatment of undulant fever, for example, due to Brucella abortus one must remember that the offending organism is residing intracellularly in many cases, and recovery must in great measure depend on the patient's natural defense mechanisms. Austrian[16] has stressed that excessive amounts of fluid should not be given because they may lead to too rapid excretion of specific antibacterial drugs. Antibacterial action of several antibiotics is increased at temperatures above 98.6 Fahrenheit and because the temperature curve is one of the most valuable indices of the success or failure of therapy, attempts to lower the patient's temperature with febrifuges are usually unnecessary and often undesirable. With fulminating infections of certain types, particularly meningococcal infections producing meningococcemia, or overwhelming pneumococcal or salmonella infections, doses of 50 to 100 cc of aqueous adrenal cortex extract or 25 to 50 mgms. of hydrocortisone given intravenously every six hours may be administered until clinical improvement results. Recent reports have shown beneficial effects of the use of cortisone and A.C.T.H. in the treatment of pneumococcal meningitis. However, corticotropin and adrenal steroids should not be employed for their antipyretic effect, for they may interfere with the mobilization of leucocytes at the side of the primary infection. If lowering the patient's temperature is judged necessary, tepid alcohol sponge baths are the procedure of choice.

d. *Antibiotic.* To what is the etiological agent sensitive and what is its sensitivity? The latter is extremely variable, and with certain organisms particularly, sensitivities should always be determined, viz. Klebsiella, Haemophilus, Staphyloccus, Mycobacterium tuberculosis, Enterococcus or coliform organisms. It is interesting that pneumococcus is seldom seen to develop penicillin resistance. Although over a hundred antibiotics are recognized at present, clinical interest is centered in relatively few. Of the fungus and mold products, industrial output has been limited largely to penicillin, streptomycin, chloromycetin and the tetracyclines—aureomycin, terramycin and tetracycline; and to tyrothricin, bacitracin and the polymyxins of bacterial origin. I do not propose to discuss each antibiotic in any detail. The most recent additions to the antibiotic armamentarium are those derived from the Actinomycetes which include actinomycin, streptomycins, chloramphenicol, neomycin,

tetracyclines, erythromycin, carbomycin, viomycin, trichomycin, nistatin, candidin and streptonivicin. Commercial trade names add much to the confusion of this list. Oleandomycin is known also as Romicil or Matromycin. Spiromycin is also known as Rovamycin, Ristocetin as Spontin and so on. Most of the latest additions to this list are primarily active against gram-positive organism. Recently a new antifungal antibiotic, Pimaricin[17] is reported from Holland to be effective in vitro against a wide variety of pathogenic and non-pathogenic fungi and species of yeast. Clinical evaluation is in progress. A new antibiotic active against a wide range of organisms was described by Zief, known as sulfocidin,[17] which acts against gram-positive and gram-negative bacteria, Mycobacteria and fungi. It was reported to be strongly bacteriacidal to gram-positive bacteria. A new group of lymphotrophic antibiotics known as the antibiolymphins is being studied. They show an increased affinity for the lymphatic system as has been demonstrated by Malek of Prague.[17]

It might be in order to mention a few highlights with respect to the use of specific antibiotics.

First, it has been shown that oral penicillin is equal to parenteral penicillin in rheumatic fever prophylaxis if the patient co-operates and takes medication as prescribed. Bio-synthetic penicillin V (phenoxyl methyl penicillin) is suitable for oral use as it can survive the acid of the stomach. It has been shown that stubborn urinary tract infections resistant to antibiotic therapy responded to methionine when it was given alone or in combination with other therapy. Kass of the Harvard Medical School found methionine to act as a urinary acidifier capable of reducing both the pH and the bacterial count of urine. Following methionine administration the urine contained an antibacterial substance. The nature of this antibacterial substance is not yet clear. Professor Garrod of England has summarized in a practical way some of the specific indications for certain antibiotics. For instance, he suggests that penicillin be used for erysipelas, scarlet fever or any streptococcal infection, as well as lobar pneumonia, gonorrhoea, syphillis and actinomycosis; streptomycin is the drug of choice for tuberculosis, plague and tularemia; chloramphenicol for typhoid; the tetracyclines for typhus and other rickettsia diseases, as well as undulant fever. (Novobiocin has recently been reported to be highly effective in the treatment of undulant fever;) Nistatin combined with sulfonamides for Histoplasma; and Nistatin alone for Candida albicans (Monilia infections). I should like also to add that in cases of ornithosis and psittacosis the tetracyclines are the drug of choice. Penicillin, bacitracin and streptomycin are essentially bacteriacidal antibiotics, and the tetracyclines, chloramphenicol, erythromycin and novobiocin are potentially and primarily bacteriostatic drugs. Sulfadiazine still holds high place in the treatment of meningococcal meningitis and the bacillary dysentery group of organisms known as the Shigellae. Penicillin resistant or sulfonamide resistant strains of Meningococcus (Nesseria meningititis) have to my knowledge not been encountered. There is no substantial evidence of any increased resistance to penicillin or other antibiotics among strains of gonococcus in spite of extensive use of these agents. Pyogenic staphylococci are becoming resistant to erythromycin particularly strains isolated in cases of suppurative endocarditis when this agent is used. Resistant strains of Streptococcus viridans developed in originally susceptible ones has been remarkably infrequent except in cases of subacute bacterial endocarditis treated with erythromycin. Since mention-

ing subacute bacterial endocarditis Finland has announced that evidence to date confirms that treatment of the pregnant patient with active subacute bacterial endocarditis has proved as successful as in the non-pregnant one, with cure of the mother and successful delivery of a living child in the majority of cases.[18]

Here I should like to present a few general remarks borrowed from two publications by Murray[19 20] which I feel emphasize the necessity for great care in the administration of antibiotic and chemotherapeutic agents. He states that we, as physicians, must remember that the "living agents of disease whether it be bacteria, fungus, rickettsia or virus, are still actively following the processes of evolution, and anything may come of it. Some of our procedures, as practised, may even help and encourage disease and might disorganize our systems and controls to loose upon us pestilences no less severe than those plagues of the past. There is plenty of evidence that certain kinds of bacteria which a few years ago were very susceptible to an antibiotic occur now as completely resistant members of the same species and cause as much or more trouble in certain cases than they did before. In some ways we are damaging ourselves by diminishing bacteria in certain situations that help us, thereby favoring others that harm us. Part of this question of environment is the disturbance of regional ecology by the use of antibiotics. The finding of known bacteria in unusual places such as Escherichia coli in the nasal pharynx and Proteus in large numbers in the stools is not necessarily merely resistance to the antibiotic, but is as likely due to the profound change in the environment by the disappearance of the expected kinds from accustomed places." I have heard Professor E. G. D. Murray of McGill University suggest to his clinical colleagues that their "indiscriminate use of antibiotics causing displaced bacterial populations may yet so confuse the patient that he will not know which end to put his hat on." Petersdorf and others have stated that prophylactic antibiotic therapy is of no benefit and distinctly hazardous in unconscious patients. They discourage the widespread prophylactic use of antibiotics for any and all situations, particularly in the light of repeated demonstrations of their failure to prevent infections. They stress that therapy of complications in surgical and medical cases should be instituted as they occur. Careful observation of the patient and vigorous treatment of intercurrent infections (as soon as they are recognized) with drugs specifically directed against their causative agents appears to be the only reasonable course to pursue, and will probably yield the best results in the long run.[21]

"The function of an antibiotic in the cell of its origin is still unknown, and what is involved in susceptibility and resistance to antibiotics is at present little more than conjecture. Further, the question of augmentation or of inhibition of one antibiotic by another requires explanation. The multiferous use of antibiotics has introduced complications that are not always easy to cope with. First, the bacteriologist is beset with difficulties in isolating the causal organism from a specimen and is further burdened with tests to select the most suitable antibiotic or to determine its levels in the patient. But these are technical matters and there is little that he can do to prevent the immediate and unguided use of drugs which may by chance effect a spectacular cure even without a diagnosis having been made. Recognizing the situation, the bacteriologist has to take note of changes in the regional flora, of the incidence of antibiotic resistant forms, of the increase in hospital cross-infection (partly due to lapses in technique from a false sense of security the clinician finds offered by the

wonder drugs) and perhaps changes in character of well known pathogens. Bacteria are responsive living organisms as subject to evolution now as in ages past. Their generation time is rapid and the use of a wide range of potent antibiotics is extensive in some parts of the world."[19 20] It is said that nearly fifty percent of all prescriptions sold over the counter in drug stores throughout the country are now made up of antibiotics.

In support of this fearful state of affairs are the numerous reports of such conditions as super-infections causing fatal staphyloccus enterocolitis. The development of diarrhea in a patient under treatment with a broad spectrum antibiotic particularly the tetracyclines, or combination of penicillin and streptomycin, should lead one to suspect the condition. In the majority of cases the diarrhea decreases when the antibiotic is discontinued. If a gram-stained fecal smear reveals gram-positive cocci, and there is deterioration in patient's condition, erythromycin or novobiocin should be administered while awaiting sensitivity tests on the offending organism, or ristocetin (isolated from the fermentation of Nocardia lurida) administered intravenously. Welch of the United States Federal Drugs Administration reports twenty-six deaths in seventy-four such cases. Further, in respect to this world-wide and statistically increasing complication of wide spectrum antibiotics, I should like to refer to a few remarks by Jawitz of the University of California in delivering the first Randall lecture at the 5th Annual Symposium on Antibiotics in Washington in October of last year, the title of which was "Patient, Doctor, Drug and Bug." On the problem of resistant staphyloccus organisms in hospital environment, he suggested "rigid asepsis, restrained use of all antibiotics, with careful selection based on the etiological agent, restriction of one antibiotic for use against organisms rapidly developing resistance." The frequency of staphyloccus resistance to an antibiotic may not be directly related to the frequency with which the antibiotic has been used in hospital. Narrow spectrum antibiotics and those which inhibit the majority of staphylococci in hospital are preferred for therapy in an effort to avoid spread of hospital infections by resistant staphylococci. During this symposium[17] Griffith reported that ordinary street staphylococci are not becoming more resistant to antibiotics, and he stated that erythromycin was more effective against the greatest number of coagulase positive strains of staphylococci recovered from nose and throat of healthy individuals. Further examples of complications of antibiotic therapy are numerous and must be considered intelligently. Severe reactions do occur, and Welch reports that among 3,419 case histories of reactions evaluated over a three year survey of 827 hospitals, and interviews with 1,637 physicians, life-threatening reactions numbered 1,072, including 809 with anaphylactoid shock, 107 super-infections, 70 severe skin reactions, 46 blood dyscrasias and 38 with angioneurotic oedema accompanied by cerebral and respiratory involvment. With the indiscriminate use of wide spectrum antibiotics, vitamin deficiencies, stomatitis, glossitis, colitis and vulvo-vaginitis are not uncommonly seen. There is no doubt, in the light of this knowledge, that the clinician today must not fail to recognize the possibilities of such undesirable effects as these, must not accept them as a peculiar manifestation of the presenting disease which he is treating and must be prepared to deal with them properly.

Finally, let us as physicians be ever mindful in our practises to exercise wisdom in the application of these antibacterial agents in dealing with the treatment of disease of our fellow man. In the words of Howard W. Haggard,

"so often medical history, to the physician, is a matter of hero worship. He pays his deep reverence with bowed head to Hippocrates and mumbles a line from the oath, he nods to Galen, he speaks with hushed voice of the galaxy of medical immortals in which Lister, Koch and Pasteur occupy such eminent positions." It is obvious that only through the intelligent use of these antibiotic drugs we as physicians will establish the antibiotic era in medical history as a memorable one and not only as a monument to its founders.

REFERENCES

1. Murray, E. G. D., American Scientist 42:1, 1954.
2. Emmerich, R. and Low, O., Z. Hyg. Infect. Kr. 31: 1, 1897.
3. Fleming, A., Brit. Jour. Exper. Path. 10:226, 1929.
4. Abraham, E. P. and Chain, E., Nature. 146:837, 1940.
5. Chain, E., Florey, H. W., et al, Lancet. 2:226, 1940.
6. Starkey, H., and Denton, G. D., Treat. Serv. Bull. July-August, 1950.
7. Vuillemin, P. Antibiose et symbiose. Assoc. Franc. pour l'avance de sc. Part 2:525-543, 1889.

7a. Ward, M. H., Symbiosis. Ann. Bot. 13: 549-562, Dec. 1899.

7b. Waksman, S. A. Microbial antagonism and antibiotic substances. The Commonwealth Fund, New York, 1945.

7c Goldstein, A., N.E.J.M. 240: 3, 4, 5, 1949.

8. Pyle, M., Proc. Staff Mayo Clinic 22: 465, 1947.
9. Yegian, D. and Vanderlinde, R. J., J. Bact. 56: 177, 1948.
10. Demeric, M., J. Bact. 56: 63, 1948.
11. Jawetz, E., et al, Science 111: 254, 1950.
12. Jones, W. F., and Finland, M., N.E.J.M. 257: 11, 12, 1957.
13. Kellow, W. F. and Dowling, H. F., Arch. Int. Med. 100: 322-330, 1957.
14. Haas, R. C. et al, N.E.J.M. 256: 152-155, 1957.
15. Eagle, H., Ann. Int. Med. 28: 260, 1948.
16. Austrian, R., J.A.M.A. 163: 12, 1957.
17. Fifth Annual Antibiotic Symposium, Washington, D. C., Oct. 1957.
18. Finland, M., N.E.J.M. 253: 22, 23, 1955.

18a. Finland, M., N.E.J.M. 250: 419-428, 1954.

19. Murray, E. G. D., American Scientist 42: 1, Jan. 1954.
20. Murray, E. G. D., The Lancet. Jan. 30, 1954.
21. Petersdorf, R. G., et al, N.E.J.M. 257: 21, Nov., 1957.
22. Haggard, H. W., The lame, the halt and the blind, Blue Ribbon Books, Inc., New York, 1932.

Procloperazine*

Procloperazine, a recently developed analogue of chlorpromazine, shows great promise in the treatment of the mild mental and emotional disturbances commonly seen in every day practice and treated on an ambulatory basis. It is particularly valuable for the many cases in which psychoneurotic symptoms make treatment of the primary disease less effective. In the recommended low dosage (usually 10 to 30 mg. a day) this drug was found to have few effects except mild drowsiness.

*Vischer, T. J., New England Journal of Medicinel 256: 1957.
Medical Abstracts, August, 1957.

Lipid Metabolism

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LIPIDS are commonly defined as fats and related substances which are insoluble in water but soluble in fat solvents such as ether, chloroform, alcohol and benzene. The lipids which are of physiological interest may be classified as follows:

1. Simple Lipids
2. Compound Lipids
3. Associated Lipids

(1) *Simple Lipids*—These are the neutral fats or triglycerides. Triglycerides are formed from one molecule of glycerol and three molecules of various fatty acids. Fatty acids may be saturated or unsaturated. This is based on the double bond linkage between the carbon atoms. Those that are saturated have no double bonds. Unsaturated fatty acids are liquid and by hydrogenation at the double bonds become saturated and solid or hardened. The essential fatty acids which cannot be Synthesized in the body or only to a small degree are unsaturated. Linoleic, linolenic, and arachidonic acid can correct deficiencies in rats. Many marine and vegetable fats contain these essential fatty acids, whereas the highly saturated animal fats do not. Arachidonic acid can be synthesized in the body from linoleic acid but vitamin B-6 is required for its conversion.

Neutral fat occurs in only 2 types of cells.

(1) In liver cells, (2) In fat depots.

(2) *Compound lipids*—These are complex compounds formed from fatty acids, glycerol and various nitrogen containing bases, and they often contain phosphate groups. They are an integral part of the general cell structure and are present in large amounts in nervous tissue.

(a) **Phospholipids**—These include lecithins which have choline as a nitrogenous base, and cephalins which contain ethanolamine. Choline is important as a lipotropic factor preventing fatty liver and in addition lecithins are important in circulating plasma as a mobilizer of the fats to and from the liver. Cephalins do not play as important a part in transport of lipids but are important in blood coagulation.

(b) **Sphingomyelins**—These contain choline but no glycerol group. Little is known of their physiological significance although they are widely distributed in brain, lung, spleen, kidney, liver and muscle.

(c) **Galactolipids**—These contain galactose but no phosphate or glycerol. They are found abundantly in nervous tissue.

(3) **Associated Lipids**—There are two main types—

(a) Split fats—which are obtained by hydrolysis of lipids, i.e. glycerol, fatty acids and soaps.

(b) Components that are associated with lipids in tissue extracts. These are mainly (i) steroids—i.e. the hormones of ovary, testis and adrenal cortex; cholesterol esters; and (ii) fat soluble vitamins.

Sterols—Cholesterol is the chief but not the only member of the sterol group found in animals. It occurs in all body tissues and appears to be one of the essential constituents of all cells. Cholesterol occurs partly in a free form and partly esterified with fatty acid. In plasma, about 70% occurs in ester form. Cholesterol actually never occurs free in the sense of being uncombined but whether free or in the ester form is always bound with protein.

Dihydrocholesterol is also present with cholesterol in tissues usually to extent of 1 or 2%. Cholesterol and dihydrocholesterol are excreted in the bile but only the former is reabsorbed. Dihydrocholesterol is a highly saturated sterol.

Now fatty acids are contained in all the three types of lipids but there is a highly significant difference in distribution. Cholesterol esters contain highly unsaturated fatty acids, phospholipid fatty acids are moderately unsaturated and neutral fat contains very little unsaturated fatty acids.

DIGESTION AND ABSORPTION OF FAT:

A small amount of fat may be digested in the stomach by means of gastric lipase however the main digestion of fat occurs in the small intestine. It is accomplished chiefly by pancreatic lipase. Digestion of fats is greatly accelerated by emulsification and this is accomplished by products of fat digestion. These complexes of bile salts and fatty acids are water soluble and can pass through the intestinal epithelium. The bile salts probably also act upon cholesterol and the fat soluble vitamins to enable them to be water soluble.

The end products of fat digestion are:

(1) Neutral fat in finely emulsified state—
(2) Water soluble fatty acid—bile acid complexes
(3) Lower glycerides—some soluble and some emulsified.
(4) Glycerol

It is generally accepted that the water-soluble products (fatty acid-bile acid complexes and glycerol) are absorbed directly into the portal blood. The emulsified but water-insoluble neutral fat is absorbed via the lining epithelial cells of the intestine into the lacteals and then into thoracic duct and so reach the venous blood. This is the "partition hypothesis" of Frazer.

These lipids carried in the blood stream may be deposited as storage fat in adipose tissues; may have temporary storage and alteration in the liver; or may undergo oxidation in the tissues. In the fat depots the lipid is chiefly neutral fat. It's chief function is to provide a large reservoir of food for the body. Protein is not stored in the body and carbohydrate has limited storage in the liver as glycogen and only lasts a few hours during starvation, hence fat is the main source of reserve energy.

The liver plays an important part in lipid metabolism. There is constant movement of fats to and from the fat depots and the tissues with the liver acting as a way station. Unsaturated fatty acids are selectively collected by the liver for formation into phospholipids and cholesterol esters. These phospholipids are supplied to tissue cells for incorporation into their structural

elements and as a slow fuel for their oxidation processes. Tissue cells cannot utilize neutral fat. Phospholipids, especially lecithins, help to mobilize neutral fats from the liver for their return to adipose tissue. The liver also synthesizes cholesterol and esterifies part of it. Fatty acids are to some extent normally oxidized in the liver to acetic acid and enter the Krebs cycle to be burned for energy.

The Normal Values of Plasma Lipids are:

(i) Neutral fat and fatty acids 200-450 mgm/100 cc

(ii) Lecithin and other Choline containing phospholipids 150-250 mgm/100 cc

(iii) Free Cholesterol and Cholesterol esters (70% in ester form). 150-250 mgm/100 cc

Now in the blood these lipids are chiefly carried in combination with protein. The "chylomicrons" are the microscopic visible physical forms of neutral fat and fatty acids stabilized by a protein film. On the other hand cholesterol and phospholipids are combined with alpha and beta globulins and are microscopically invisible macro-molecules.

These giant molecules have molecular weights greater than 1,000,000. Using electrophoretic methods considerable study has been given to the alpha and beta lipoproteins. The most significant difference appears to be the ratio of cholesterol to phospholipid in each lipoprotein.

In alpha lipoproteins the cholesterol-phospholipid ratio has been found to be 0.55 and in beta lipoproteins over twice as high about 1.25. Approximately 75% of the serum cholesterol is found in the beta lipoprotein fraction.

Studies have revealed that there is a tendency for a reduction in alpha lipoproteins and increase in beta lipoproteins with advancing years. However, there is a sex difference in that in women these changes usually begin about 13 years later than in men and last longer until by about the sixth decade there is little difference in the lipoproteins between the sexes. This has been attributed to sex hormones. It has also been shown that in patients who have evidence of atherosclerosis there is this reduction of the alpha fraction and rise in the beta fraction. Furthermore, the administration of oestrogens has been found to reduce the beta lipoproteins in survivors of myocardial infarctions and administration of testosterone has produced an increase in the beta fraction.

The lipoproteins have been studied in diseases which are associated with elevated serum cholesterol levels and again an increase in beta lipoproteins and decrease in the alpha portion is generally the rule. These diseases include diabetes mellitus, xanthoma tendinosum and tuberosum and hypo-thyroidism. The most significant changes are noted in the nephrotic syndrome.

Another method of studying the lipoproteins is by means of the ultracentrifuge. This has been pioneered by Gofman from the Donner laboratory in California. The ultracentrifuge uses great gravitational forces, and large molecules of the size and weight of protein can be made to undergo sedimentation or flotation depending on their density in the medium in which they are suspended. The rate of movement of sedimentation or flotation can be observed and measured. The unit of sedimentation has been designated as the "S" unit in honour of Svedberg, and Gofman has designated the flotation rates as Sf units.

Gofman measures the lipoproteins according to their rate of migration under four groups.

(1) Sf 0-12, (2) Sf 12-20, (3) Sf 20-100, (4) Sf 100-400. At present it is felt that all of these groups are of significance in atherosclerosis but the Sf 20-100 and Sf 12-20 groups are most frequently elevated. Gofman feels that he can predict the likelihood of the development of clinical atherosclerosis. In Oct. 1956, the report of the Technical group of the Committee on lipoproteins and Atherosclerosis showed that the serum cholesterol, the Sf 20-100 lipoproteins and possibly the Sf 12-20 group were elevated prior to clinical recognition of atherosclerosis. Now Gofman and his group stated in this report that statistically it was possible to predict the development of atherosclerosis, while on the other hand the group from Cleveland, Harvard and Pittsburg felt that it was not valid to predict statistically and they stated that the lipoproteins measurement have no value over measurement of serum cholesterol in coronary artery disease.

In recent years important knowledge of lipid metabolism and its relation to atherosclerosis has come from epidemiologic studies of the incidence of atherosclerosis in various populations and its correlation with serum and dietary lipid levels.

The death rate from atherosclerosis has shown a consistent rise in the United States and Great Britain during the past twenty-five years. There was a similar trend in the Scandinavian Countries until the early 1940's, when there was a transitory reversal of this trend. This development occurred during World War II when there was a deterioration in food supplies, particularly dairy and animal products. When the dietary lack was replaced following the war the death rate from atherosclerosis again began to rise. It is interesting that during the same period in Denmark, there was no change in their diet and also no change in the death rate. In Germany the same trend has been observed, except that during 1946-1947, there was a great shortage of fats and incidence of death rate from atherosclerosis fell in 1947-1948, but now has risen again and is showing the upward trend.

In some countries, notably the British Isles, it has been shown that atherosclerosis has a higher incidence in the economic upper classes. This has been attributed to the ability to obtain higher priced foods such as dairy and meat products. This has not been the finding on this continent possibly as the standard of living is more uniform.

Other epidemiological studies have shown that the incidence of atherosclerosis varies in different populations. It is high in the United States and Great Britain but low among native populations of China, Japan, Indonesia and Negroes of Kenya and South Africa. Among American Negroes and Japanese, the incidence of atherosclerosis is much higher. Ancel Keys is doing the major study in this field on this continent; he has studied the native Japanese, the Japanese in Hawaii and in Los Angeles. Here the incidence in the same racial stock varied greatly. It is rare in Japan, moderately frequent in Hawaii and about as frequent in American Japanese as white population. These American Japanese were second generation Nisei. He has also found that among populations with low fat intake, there are invariably low values of serum cholesterol and beta lipoproteins and low incidence of atherosclerosis. The level of cholesterol in the diet itself has little effect on serum cholesterol levels, as the liver can synthesize it. However, by lowering total fat content of the diet the serum cholesterol level will fall.

On the other hand some studies have shown the effect of different fats on the serum cholesterol levels. Bronte-Stewart and co-workers from the

University of Cape Town have studied the effect of different dietary fats on serum lipids in a small series on Bantu natives and the white population. It was found that animal fats increased the serum cholesterol and B lipoprotein levels, whereas vegetable and marine oils decreased or produced no change in the lipid levels. In addition, it was found that the unsaturated fractions of the fatty acids of vegetable and marine oils would cause a fall, whereas saturated fractions would elicit an increase in lipid levels.

Since 1913 when Anitschkow and Chalatow by feeding cholesterol, produced arterial lesions in the rabbit, great interest has centered upon the importance of cholesterol and other lipids in the pathogenesis of atherosclerosis.

The gross and microscopic appearance of lesions in experimentally induced atherosclerosis in rabbits and naturally occurring atherosclerosis in humans are remarkably similar. The chief difference is the lack, in human atherosclerosis, of conspicuous accumulations of lipids in the cells of the reticuloendothelial cells of the involved arteries (this is prominent in the rabbit). Also the distribution of the atheromatous lesions in the rabbit are confined to the aorta, its branches and the pulmonary arteries. In man lesions are prominent in the aorta, its branches, and the cerebral and retinal arteries, the pulmonary arteries being rarely involved.

Experimental cholesterol atherosclerosis has been produced in fowl, guinea pigs, and also dogs by the addition of thiouracil. Cats and rats have been resistant to the development of atherosclerosis. So there is a species difference in the susceptibility to cholesterol induced atherosclerosis.

Another important observation is that esxperimentally induced atheromatous lesions can be prevented from developing or caused to regress by factors affecting lipid metabolism.

McMeans and Klotz have shown that lipoid deposits in the aorta could be made to disappear if cholesterol feeding was discontinued. The severity of atheromas appeared to be decreased if polyunsaturated fatty acids were used in place of stearic or oleic acids as the vehicle for the cholesterol in the diet although hypercholesterolemia was not reduced.

Cholesterol induced atheromata have been inhibited by administration of thyroid extract and oestrogens. In diabetic rabbits produced by alloxan, cholesterol feeding produces significantly less atherosclerosis. Also it has been claimed that administration of adenosine triphosphate, potassium thiocyanate or cortisone have inhibited cholesterol induced atherosclerosis. Regression of cholesterol atherosclerosis has been demonstrated upon withdrawal of added cholesterol from the diet. The addition of dihydrocholesterol to a diet rich in cholesterol prevented the development of hyperlipemia and reduced the severity of atherosclerosis in the birds. Dihydrocholesterol is a plant sterol and is believed to act through interference with cholesterol absorption. This is the basis for use of beta sitosterol, a plant sterol in treatment of human atherosclerosis and hypercholesterolemic states.

It has been shown quite conclusively that in certain disease states that are associated with abnormal serum lipids, there is also an increased incidence of atherosclerosis. Thus in familial hypercholesterolemia in addition to xanthoma of the skin and connective tissues there is atheroma of the coronary arteries and the aorta. The cause of death in this group is commonly that of coronary occlusion. In these cases there appears to be an inborn error of cholesterol metabolism. Hypothyroidism is accompanied by elevation of serum cholesterol levels and again these patients often die with evidence of

atherosclerosis. In diabetes mellitus there is twice the incidence of atherosclerosis in males and three times the incidence in females compared to the general population. It has been found in all these conditions that the beta lipoproteins are elevated as well as Sf 20-100 lipoproteins.

The experimental, epidemilogic, pathologic and laboratory studies have shown that atherosclerosis is in some way related to a disorder in lipid metabolism. The exact mechanism has not yet been elicited but as more information becomes known about lipid metabolism, perhaps a solution to this problem of atherosclerosis may not be too long in emerging.

REFERENCES

1. Keys, A., Anderson, J. T., Mickelsen, O., Adelsow, S. F., and Fedanza, F.. Diet and serum cholesterol in man, lack of effect of dietary cholesterol. Jour; Nutrit 59(1) 39-56, 1956.
2. Sinclair, H. M., Deficiency of essential fatty acids and atherosclerosis. Lancet, Lond. 270(6919) 381-303, 1956.
3. Bronte-Stewart, B., Antonis, A., Eales, L., Brock, J. F.; Effects of feeding different fats on blood cholesterol level. Lancet, Lond. 270 (6922) 521-526, 1956.
4. Heuper, W. C., Pathogenesis of atherosclerosis, Amer. J. Clin. Path. 26(6), 559-578, 1956.
5. Dock, W., Causes of arteriosclerosis, Bull. N. Y. Ac. of Med. March, 1958.
6. Dock, W., Arteriosclerosis—some clinical implications Am. J. Med. 11(6): 730-735, 1951.
7. Davidson, J. D., Diet and lipotrophic agents in arteriosclerosis. Am. J. Med. 11(6): 736-748, 1951.
8. Gould, R. G., Lipid Metabolism and atherosclerosis, Am. J. Med. 11: 468-479, 1951.
9. Russ, E. M., Eden, H. A. and Barr, D. P.; Protein lipid relationship in human plasma in normal individuals. Am. J. Med. 11: 468-479, 1951.
10. Farquhar, J. W., Smith, R. E., Dempsey, M. E.; The effects of beta-sitosterol on serum lipids of young men with arteriosclerotic heart disease; Circulation, N. Y. 14(1): 77-82, 1956.
11. Buzina, R., Keys, A.; Blood coagulation after a fat meal; Circulation, N. Y. 14(5): 854-858, 1956.
12. Robinson, R. W., Hegano, N., Cohen, W. D., Sniffen, R. C., Aherer, J. W. Jr., Effects of oestrogen therapy on hormonal functions and serum lipids in men with coronary atherosclerosis; Circulation, N. Y. 14(3): 365-372, 1956.
13. Evaluation of serum lipoproteins and cholesterol measurements as predictors of clinical complications of atherosclerosis, results of a cooperative study of lipoproteins and atherosclerosis; Circulation, N. Y. 14(4): Part 2, 691-742, 1956.
14. Schroepfer, G. J., Jr., Lipid factors in atherosclerosis, N. England J. Med. 257 (26): 1275-1279, 1957.

The Pharmacological Basis Of Antihypertensive Therapy

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THE treatment of essential hypertension is strictly an individualized procedure, calling for patience and persistence on the part of both physician and patient. It usually involves several forms of therapy one of which may be the use of antihypertensive drugs. In fact, the majority of these patients are given a trial with hypotensive agents at some time during the course of the disease. Considerable time may be required to work out the most satisfactory procedure for managing any particular case and even then frequent revision is usually necessary. It is not essential to seek immediate dramatic results except in the case of malignant hypertension or in those patients in whom the pressure is so elevated as to threaten a cerebrovascular accident.

Today, quite a variety of hypotensive agents are available to the physician. However, this does not mean that the situation with regard to the drug therapy of hypertension is a happy one—far from it. There are several reasons for this. In the first place, these drugs do not alter the underlying defect responsible for the disease—of which elevated blood pressure is but one manifestation. Secondly, reduction of blood pressure is not **always** accompanied by relief of symptoms. Indeed, in some cases, symptoms may be aggravated. It was this fact that led many to the conclusion that elevated blood pressure was actually essential for bodily functions in the face of the existing pathology. However, this view is not as widely held as it once was and most authorities now agree that if treatment is begun early enough the complications of prolonged hypertension may be arrested or at least delayed. Thirdly, all potent antihypertensive drugs have distressing and sometimes serious side effects and their prolonged use may have a detrimental effect on vital organs. Lastly, antihypertensive therapy in those cases showing marked impairment of renal function is especially hazardous and the use of powerful hypotensive drugs may contribute to a fatal outcome. In this connection, Wilson and Abrahams (1) suggest that in hypertension associated with primary renal disease the use of hypotensive drugs may result in further deterioration where blood urea is over 60 mg. per cent and creatinine clearance below 35 ml. per minute. On the other hand, when there is only slight renal impairment, hypotensive therapy may retard further deterioration and retinal vascular damage may be prevented for a few years. The difficult problem of evaluating antihypertensive procedures has been discussed by Corcoran and his associates (2).

Now, the exact etiology of essential hypertension is still not known. However, we do know that it is often possible to effectively lower the blood pressure of hypertensive patients by interrupting or reducing the vasoconstrictor impulses flowing over the sympathetic nervous system to the blood vessels. These impulses are vulnerable to pharmacologic attack at several different

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sites, namely, the cerebral cortex; sympathetic centers in the hypothalamus; the medullary vasomotor center; sympathetic ganglia, and the blood vessels themselves. Moreover, we now have drugs that exert their primary action at one or other of these sites. These drugs may be effective alone, but more often they are used in various combinations.[3]

SEDATIVES

The function of sedation is an obvious one and requires little comment. The cardiovascular system is very sensitive to emotional stress and so, by sedating the patient, we remove at least partially, the strong contributing factor of nervous tension. The drugs most frequently used are phenobarbital, bromides and the famous or infamous tranquilizers such as meprobamate (Miltown, Equanil). It need hardly be stated that all of these must be employed with discretion. Their use may lead to psychic dependence. True addiction can result from the use of barbiturates but this should not occur—if the patient adheres to the prescribed dosage. Moreover, it cannot be emphasized too strongly that sedative drugs cannot substitute for a sensible, well organized way of life and that a placebo may prove to be equally as effective in many cases. Phenobarbital is usually given in a dose of 15 mg. three or four times a day. Occasionally, when periods of unusual stress are anticipated, sodium pentobarbital (nembutal) may be substituted to advantage. The usual dose of meprobamate is 400 mg. three times a day. This drug is an effective tranquilizer and muscle relaxant and may be of definite value in mild cases.

RAUWOLFIA

Rauwolfia preparations may be regarded as sedative-hypotensive compounds and treatment of hypertension is very often instituted with these drugs. They have both central sedative and hypotensive actions—neither of which is well understood. The sedative or tranquilizing effect is distinctly different from the sedation produced by the barbiturates and this difference is reflected in the electroencephalographic pattern observed after the two drugs. The EEG is not altered by Rauwolfia. The hypotensive action is believed to be due primarily to inhibition of sympathetic centers in the hypothalamus and to inhibition of the medullary vasomotor center[4]. This removal of sympathetic dominance results in a relative vagotonia. Bradycardia is observed which may contribute to the hypotension but is not essential to it. The Rauwolfia compounds do not exhibit ganglionic blocking or significant peripheral adrenolytic activity. The fall in blood pressure appears to be the result of decreased vascular resistance. It is not prevented by atropine or vagotomy. The hypotension does not result from augmentation of afferent depressor reflexes as is the case with veratrum. The more intimate mechanism of action is still being investigated. When administered orally, they are not potent, rapidly acting drugs. Their action is mild and with small dosage, several weeks may be required for the full effect to develop. Increasing the dosage tends to increase the duration of action rather than to intensify it. When administered parenterally, the hypotensive action may be observed in two to three hours, the rapidity and duration of action depending on the dosage. Following a course of therapy, the effect persists for some time after withdrawal of the drug. Rauwolfia compounds have two chief uses (1) the management of mild cases—in which they may be adequate alone and (2) as background drugs for treat-

ment with the more potent antihypertensive agents. In this capacity, they tend to relieve anxiety and headache and also to counteract some of the undesirable effects of the more powerful drugs. Rauwolfia preparations themselves are not entirely free of side effects. However, these are usually mild and reflect diminished sympathetic activity or what amounts to parasympathetic dominance. The two most troublesome symptoms are referable to the nasal mucosa and gastrointestinal tract. Nasal stuffiness is a very common complaint. If it is unduly annoying, an antihistaminic may be prescribed. However, this side effect usually diminishes with continuing treatment and may even clear up completely after a few months. Increased gastric secretion and gastrointestinal hypermotility are observed with Rauwolfia. The former may be relieved by atropine or antacids while the latter rarely requires treatment. There is one other side effect that is much more serious and for which the physician must be constantly on the alert. Severe mood depression is seen in some patients and there are numerous reports of attempted suicide. This situation calls for immediate withdrawal of the drug and usually vigorous and prolonged psychotherapy. Three types of preparations are available to the physician (1) the pure alkaloid reserpine (Serpasil, Serpaloid) (2) alkaloidal concentrates (Rauwiloid, Rautensin) and (3) extracts of the whole root (Raudixin). The relative potencies of these three preparations are in the ratio of 1:4:250 with the pure alkaloid being the most potent. Reserpine is truly a powerful drug and as little as 0.05 mg. per day may be adequate. The average maintenance dose appears to be about 0.25 mg. per day.

HYDRALAZINE (APRESOLINE)

This drug is a potent vasodilator but the exact mechanism of action is still in doubt. Both central and peripheral factors appear to be involved. Some investigators attribute its action largely to its ability to inhibit such pressor substances as pherentasin, angiotonin and hypertensin. It mildly antagonizes the vasoconstrictor effects of the catecholamines adrenaline and noradrenaline. Hydralazine is claimed to be rather unique in that it lowers arterial pressure without reducing renal plasma flow. However, the clinical usefulness of this compound has been limited by the severity of its side effects, notably tachycardia and severe occipital headache. The cardiac acceleration causes undue cardiac strain and persistent angina pectoris may result. The headache may be intolerable. The severity of these side effects may be greatly reduced by combining the drug with Rauwolfia and by employing the minimal effective dosage. The initial dose is 10 mg. four times a day. It may be necessary to increase this gradually to a maximum which probably should not exceed 200 mg. per day. Doses in excess of this may result in the appearance of a syndrome resembling rheumatoid arthritis and later, lupus erythematosus. These respond to discontinuation of the drug, but it may be necessary to administer ACTH or cortisone.

VERATRUM

The active principles of veratrum preparations are alkaloids derived principally from two species of plants belonging to the Lily family—Veratrum album and Veratrum viride. Clinically, pure alkaloids and cruder preparations are both employed. The cardiovascular actions are extremely complex. The hypotensive action is due to vasodilatation resulting primarily from inhibition of the medullary vasoconstrictor center. The action is a reflex one,

the afferent impulses being carried by vagal fibers arising chiefly from the lungs and left ventricle. Other poorly understood factors appear to be involved. Veratrum also induces reflex bradycardia which may contribute to the hypotensive action but is not essential to it. There is no ganglionic blocking or peripheral adrenolytic action nor is there any direct effect on the blood vessels. Veratrum preparations may be employed to advantage in the treatment of malignant hypertension; in the management of hypertensive crises; and in hypertension associated with toxemias of pregnancy. The chief drawback to their use is their emetic action which is observed even with parenteral administration. Unfortunately, the dose which produces nausea and vomiting is usually not too far removed from the effective hypotensive dose. Rauwolfia helps to suppress this side effect. Common preparations used are Alkavervir (Veriloid)—a partially purified mixture of veratrum alkaloids for oral use—and the pure alkaloids Protoveratrine A and B for both oral and parenteral administration. The dosage must be carefully adjusted to the individual patient. A usual starting dose is 2.0 mg. of Veriloid or 0.25 mg. of Protoveratrine, three or four times a day. In those cases where a very prompt action is required the pure alkaloids may be given by slow intravenous infusion. With this method of administration, it is imperative that blood pressure readings be taken at frequent intervals.

GANGLIONIC BLOCKING AGENTS

These compounds are very potent hypotensive drugs. They exhibit high specificity for ganglionic structures but little or no selectivity with respect to the ganglia affected. Consequently, they produce widespread but not necessarily complete blockade of autonomic ganglia. The effect on arterial pressure is influenced by the level of the pressure at the time of administration and by posture. Thus, in a normotensive individual in the supine position, the effect of ganglionic blockade is mild but on assuming the upright position, postural hypotension results. In the hypertensive patient, the blood pressure falls significantly even in the supine position and in the upright position, postural hypotension is greater than that observed in normotensive individuals. The fall in blood pressure produced by ganglionic blocking drugs is thought to be due primarily to decreased cardiac output. Two chief factors are involved (1) decreased venous return resulting from pooling of blood in the peripheral circulation, particularly the veins, under the influence of gravity and (2) blockade of sympathetic impulses to the heart with a resulting decrease in rate and vigour of contractions. Ganglionic blockade, of course, interferes with compensatory circulatory adjustments. Renal blood flow may be reduced but the tone of the renal arterioles appears to be maintained by autonomous intrinsic activity. Consequently, reduction in blood flow produced by ganglionic blocking agents tends to wear off even though hypotension persists. The co-existence of congestive failure greatly reduces the effectiveness of hypotensive drugs particularly the ganglionic blockers. If failure is corrected by means of salt restriction and a diuretic, their effectiveness is restored.

Dosage must be regulated on the basis of blood pressure readings taken in the upright position. Since postural hypotension is essential to the effectiveness of these drugs, they are more effective in the ambulatory patient, and at night, tilting the bed will help to maintain the action during sleep. Dosage must be adjusted frequently since tolerance develops quite rapidly, particularly during the first week of therapy. Tolerance is lost in about two weeks after

withdrawal of the drug. Consequently, if for any reason treatment is temporarily interrupted it must be resumed at a lower dosage. Side effects are inevitable, the most troublesome resulting from the blockade of the cholinergic nervous system. Blurring of vision due to cycloplegia, dry mouth, constipation and urinary retention are the most disturbing side effects. Constipation is usually severe and if untreated may progress to ileus. It must be treated early and vigorously with laxatives and a cholinergic drug, the most suitable of which is prostigmine. This drug also combats the urinary retention. Visual difficulties may require dark glasses, corrective lenses and pilocarpine locally or systemically.

Several effective ganglionic blocking drugs are available to the physician. Hexamethonium—initial dose 25 to 50 mg. subcutaneous or 125 mg. oral three times a day—has been replaced to a great extent by pentolinium (Ansolysen). This latter drug is effective in doses about one-fifth that of hexamethonium and its duration of action is about 40 per cent longer (8 to 12 hours). Chlorisondamine (Ecolid) is much like pentolinium and both are more effective orally than is hexamethonium. More recently, mecamylamine (Inversine) has been employed extensively. It has the advantages of greater potency and duration of action as well as almost complete absorption following oral administration. It may also be given parenterally. The initial dose is 2.5 mg. three times a day. Ganglionic blocking drugs can be combined to distinct advantage with Rauwolfia preparations. The latter reduce the dosage of the blocking drugs required and also tend to counteract some of their side effects, notably constipation. It should be borne in mind that ganglionic blockade is never entirely complete. Sympathetic impulses may break through and cause an elevation of blood pressure. Consequently, in times of undue stress, it may be necessary to increase the dosage. On the other hand, if the patient is able to adopt a more relaxed way of life, the dose may have to be reduced.

THIOCYANATES

Thiocyanates have had a stormy history in medical practice for over 50 years. Their use as antihypertensive drugs is a very controversial subject and they are utterly rejected by many clinicians because of their toxicity. On the other hand, others believe that they have a definite place in the treatment of hypertension, particularly in the management of hypertensive headache. There is general agreement, however, that their use should be accompanied by frequent blood level determinations. Blood levels should be kept below 15 mg. per cent. The mechanism of the hypotensive action is not known. Thiocyanates have a number of side actions some of which may be serious. These include dermatatis, conjunctivitis, nausea, anorexia, palpitation and general weakness. They also interfere with the function of the thyroid gland apparently by blocking the mechanism by which the gland concentrates iodide ion. This effect can be counteracted by administration of excess iodide in the diet. In spite of all these side effects, the fact remains that many hypertensive patients obtain greater symptomatic relief with thiocyanates than with any other drug. The initial dose of sodium thiocyanate is 100 to 200 mg. three times a day. Thereafter, the dosage can be regulated on the basis of blood level determinations.

NITRITES AND ADRENERGIC BLOCKING AGENTS

These drugs are peripherally acting vasodilators. The action of the nitrites is due to a direct depressing effect on smooth muscle whereas that of the

adrenolytic compounds is an indirect one through blockade of the sympathetic innervation of the vessels. There is no question that the nitrites can produce a marked fall in blood pressure. However, the side effects of prolonged therapy with adequate dosage are out of proportion to the results obtained. This, together with the transitory and inconstant nature of their action makes them of little value in the therapy of hypertension. Likewise, the adrenolytic drugs such as dibenamine, dibenzyline and the dihydrogenated ergot alkaloids are of little use in this condition. Some adrenolytic drugs are employed, however, in the diagnosis of pheochromocytoma.

SUMMARY

1. The treatment of essential hypertension is a strictly individualized procedure. It involves several forms of therapy one of which may be the use of antihypertensive drugs.

2. Potent antihypertensive drugs should probably not be employed in mild cases. They may be of definite value in severe cases and may arrest or delay the complications of prolonged hypertension.

3. The effectiveness of therapy should not be judged on the basis of blood pressure readings alone but also on estimates of cardiac, renal and retinal status.

4. Home blood pressure readings should be compared with office readings. Due to apprehension, some patients may escape from the effect of hypotensive drugs when visiting the doctor's office. This may mislead the physician to increase the dosage.

5. Success or failure of drug therapy may hinge on the painstaking regulation of dosage for the individual patient. Only in this way can the optimal effect be obtained with a minimum of side effects. If possible, it is always highly desirable to gradually reduce dosage.

6. Side effects are inevitable and the patient should be informed of this and of the prolonged nature of the treatment.

7. Where the use of potent antihypertensive drugs is indicated, combination therapy is usually preferable. However, the use of ready made mixtures is to be deplored since it does not permit dosage regulation of each constituent drug.

8. Finally, it should be remembered that reassurance, relaxation and a placebo will produce gratifying results in many cases of hypertension—psychotherapy is at least equally as important as pharmacotherapy.

REFERENCES

1. Wilson, C., and Abrahams, D. G., British Med. Bull. **13**, 39, (1957).
2. Corcoran, A. C., Dustan, H. P., and Page, I. H., Ann. Internal Med., **43**, 1161, (1955).
3. Moyer, J. H., G. P. **XV**, 109, (1957).
4. Bhargava, K. P., and Borison, H. L., J. Pharmacol. 119, 395, (1957).

Some Considerations In The Laboratory Diagnosis Of Coronary Artery Disease

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FOR practical purposes discussion of this subject is best treated under two headings, viz,—

(a) Coronary Insufficiency (Anginal Syndrome)
(b) Myocardial Infarction

CORONARY INSUFFICIENCY (Anginal Syndrome)

The laboratory diagnosis of the anginal syndrome consists of tests that precipitate relative myocardial anoxia and record its results electrocardiographically. The two most commonly used tests are, (1) the Anoxia Test and (2) the Master Two-Step Exercise Test. In the Anoxia Test, generalized anoxemia is induced by having the subject breathe a mixture of 10% oxygen and 90% nitrogen for twenty minutes unless cardiac pain is experienced before this interval. Electrocardiograms are recorded during this procedure and specific electrocardiographic changes, especially ST segment depressions, serve as indicators of myocardial anoxia.

In the Master Two-Step Exercise Test, the patient is connected to the electrocardiograph and a tracing (usually Lead V_4) is recorded before, immediately after, and five minutes after, strictly graduated exercise. The latter consists of a carefully controlled number of ascents and descents of a specially constructed series of steps, three in number, arranged in the fashion of a "stile," each step being nine inches high. The number of ascents and descents required is based on the patient's age and weight, and it is understood that the purpose of the test is **not** to cause cardiac pain, but to determine the electrocardiographic response to graduated exercise of a type to which most patients are accustomed. Various electrocardiographic changes are used as criteria of exercise-induced myocardial anoxia, but, in this test, as well as in the Anoxia Test, the most specific finding is depression of the ST segment.

Since both tests carry with them certain dangers, particularly that of myocardial infarction, they are not widely recommended, and can usually be avoided by the taking of a careful history; the performance of an adequate physical examination; routine electrocardiography, the presence of an abnormal resting electrocardiogram being a contra-indication to the performance of any such test; careful cardiac fluoroscopy to rule out left ventricular enlargement; assessment of response to nitroglycerin; and the discovery of extracardiac causes of anterior chest pain.

There are some physicians who prefer to avoid such tests at any cost. I feel, however, that, if strict precautions are observed, the Master Test in particular is not likely to constitute a source of danger to the patient.

MYOCARDIAL INFARCTION

There is little to offer that is new with respect to the laboratory diagnosis of myocadial infarction. As a matter of fact, what I wish to stress here is that laboratory findings in this condition, if wrongly interpreted, can confuse

issues rather than clarify them. For example, electrocardiograms must be interpreted with extreme care, and, if this is done it may be readily possible to differentiate between a myocardial infarction and other conditions which may mimic it, such as acute pericarditis, which has different electrocardiographic findings, and aortic dissection and acute upper abdominal disease, which have none. However, it is the history rather than the electrocardiogram that will aid in distinguishing a myocardial infarction from a pulmonary embolism; and when both are present, as is occasionally the case, the situation may become hopelessly confused.

As a matter of fact, it has been my experience that there is frequently too much weight placed on the electrocardiogram as an indicator of myocardial infarction, and too little attention, in doubtful cases, paid to the older, less esoteric evidences of myocardial necrosis, such as leucocytosis, elevated sedimentation rate and pericardial friction rub. One must emphasize, therefore, that in doubtful cases, the electrocardiogram is only a diagnostic adjuvant and not the final court of appeal.

Despite such admonitions, repeated at frequent intervals, it is fashionable today to continue to search for such final courts of appeal, presumably so that it will no longer be necessary to exhibit diagnostic acumen or clinical judgment. One of these so-called diagnostic aids is the determination of the presence of C-Reactive Protein. This is an abnormal serum globulin formed in response to infection, necrosis or neoplasia, and can be detected in the serum because it produces a precipitate with the C-polysaccharide of certain pneumococci. Since it is an abnormal globulin, its mere presence indicates the existence of the factors leading to its production, and quantitative determination is unnecessary. With respect to myocardial necrosis, however, its specificity suffers from the fact that infection, neoplasia, or necrosis of other organs or tissues must be ruled out.

Another laboratory "aid," which was originally described as the *sine qua non* in the laboratory diagnosis of myocardial infarction, and which is now being relegated to its proper niche, is the determination of the serum glutamic oxalacetic transaminase. This is an enzyme that is present in all tissues in greater or lesser concentrations, being most plentiful in liver, lung and muscle, especially heart muscle. It is liberated into the blood serum as the result of necrosis of any of these tissues, and can be measured by biochemical means. The figure of 40 units or higher is considered abnormal, and for some time, it was considered that the serum transaminase level was the final laboratory key to myocardial infarction.

One must emphasize, however, that the interpretation of this test has many pitfalls; and, when these are taken into consideration the area of its diagnostic utility undergoes a marked shrinkage. In the first place, in myocardial infarction, the serum transaminase returns to its normal level on the fifth day after the insult. If the test is done after that period, it is, of course, valueless. Furthermore, there are other causes of elevated serum transaminase which must be excluded. These include pulmonary embolism, acute liver necrosis and acute pancreatic disease. Worse still, it has been clearly established that opiates such as codeine and morphine may, in themselves, bring about elevation of serum transaminase levels. Since the usual diagnostic problem in such cases frequently revolves around the elucidation of an attack of retrosternal pain of sufficient severity to have required one or more doses of such opiates, it is obvious that unquestioning reliance on serum

transaminase levels will, more often than not, lead to serious and repeated diagnostic errors.

All in all, therefore, though it may seem elementary to labour this point, it must be emphasized that in myocardial infarction, as in all other medical problems, laboratory values must be interpreted with extreme caution, careful discrimination and a fine disdain for results that do not fit in with carefully-evaluated clinical findings.

Treatment of Herpes Zoster With Vitamin B_{12}*

Various drugs from time to time have been reported to be effective in the treatment of herpes zoster. They are pituitrin, sodium iodide, broad spectrum antibiotics, ACTH, cortisone, protamide, duhydroergotamine and autohemotherapy. Antibiotics like aureomycin or chloromycetin, or ACTH mitigate severity and prevent post-herpetic pain, but results are neither consistent nor spectacular. Jolles obtained excellent results with vitamin B_{12}.

In his study there were ten cases of herpes zoster, six were children. The diagnosis was established on the characteristic clinical picture: presence of initial febrile reaction associated with erythema, and pain along the cutaneous nerve root, followed by the eruption of vesicles. The affection was unilateral in all the cases and in none was there any associated disease. The patients were seen on the first or second day of onset of illness, thereafter regularly for ten days after vitamin B_{12} was started and later on once a fortnight for a period of 3-4 months to detect the occurrence of post-herpetic neuralgia. In adults, 100 micrograms daily was given for a total of four or five injections. The dosage in children was reduced to 50 micrograms for the same period. Zinc oxide powder was used for local application.

All the patients showed a dramatic response. There was marked relief after the second injection and in most cases complete relief was obtained after the fourth injection. None of the patients developed post-herpetic neuralgia.

The author feels that although there have been reports in the literature that a single injection of 1,000 micrograms vitamin B_{12} gives very good results, the small dosage employed by him is as effective.

*Srivastava, J. R., Journal of the Indian Medica Association. 27: 1956. Medical Abstracts, August, 1957.

INFECTIOUS DISEASES — NOVA SCOTIA
Reported Summary for the month of June, 1958

Diseases	NOVA SCOTIA 1958 Cases	NOVA SCOTIA 1958 Deaths	NOVA SCOTIA 1957 Cases	NOVA SCOTIA 1957 Deaths	CANADA 1958 Cases	CANADA 1957 Cases
Brucellosis	0	0	0	0	0	0
Diarrhoea of Newborn	0	0	0	0	0	0
Diphtheria	0	0	0	0	3	2
Encephalomyelitis Infectious	0	0	0	0	3	3
Food Poisoning	0	0	0	0	0	0
Gastroenteritis (1) Infectious	67	3	35	3	0	0
Hepatitis—Infectious Including Serum Hepatitis	26	0	11	0	0	0
Impetigo of Newborn	0	0	0	0	0	0
Influenza (if unusual number of cases)	195	1	336	2	428	551
Meningococcal Meningitis and Meningococcimia	0	0	0	0	21	34
Pertussis	163	0	37	0	661	575
Poliomyelitis (paralytic) non-paralytic)	0 0	0 0	0 0	0 0	9 0	6 3
Scarlet Fever and Streptococcal Sore Throat	44	0	214	0	518	676
Tuberculosis (pulmonary) (non-pulmonary)	15 4	2 1	6 0	0 0	446 42	773 53
Typhoid and Paratyphoid Fever	1 0	0 0	0 0	0 0	0 16	0 31
Venereal Disease (syphillis) (gonorrhoea)	5 15	0 0	5 48	0 0	174 1066	234 1310
Anthrax	0	0	0	0	0	0
Cholera	0	0	0	0	0	0
Psittacosis	0	0	0	0	0	0
Rabies	0	0	0	0	0	0
Smallpox	0	0	0	0	0	0
Tetanus	0	0	0	0	0	0
Trichinosis	0	0	0	0	0	0
Tularemia	0	0	0	0	0	0
Other rare diseases	1	0	0	0	0	0
Other (if unusual number of cases)	35	0	0	0	0	0

(1) amoebic and bacillary dysentery and salmonellosis

Remarks: A case of typhoid fever was reported this month in a man aged 19 years. The strain of E. typhi isolated was phage typed and found to be type B. As far as is known this type has never previously been isolated in Nova Scotia.

A proven case of generalized systemic blastomycosis dermatidides was reported in Cumberland County. The patient was treated with a new antibiotic known as Fungizone and made a miraculous recovery.

35 Cases of bronchiolitis in children with four deaths were reported from the Glace Bay area during the month. An outbreak of influenza was reported from Queens County during the month. The symptoms were reported to be similar to those of the 1951 outbreak. Of the three deaths from tuberculosis two of them were pulmonary tuberulosis in elderly persons and one was tuberculosis meningitis in a child seven years old.

There have been many inquiries from physicians over the past year about whether or not it is advisable to use antibiotics in the prophylaxis of ophthalmia neonatorum and whether the Department of Public Health should provide antibiotics for this purpose in addition to silver nitrate which is now provided. We have not yet been able to secure evidence that antibiotics are superior to silver nitrate for this purpose.

The following report of the Committee on Fetus and Newborn, American Academy of Pediatrics will be of interest in this matter.

STATEMENT ON PROPHYLAXIS OF OPHTHALMIA NEONATORUM*

On January 25, 1955, the Committee on Fetus and Newborn reviewed the problem of prophylaxis of gonorrheal ophthalmia in the newborn infant with particular reference to the possibility of changing the standing recommendations for instillation of 1% silver nitrate. At that time, review of available information indicated:

1. That no evidence existed that damage to the eyes has followed the use of 1% silver nitrate when used as recommended.
2. That use of various antibiotics (penicillin, erythromycin) instead of silver nitrate did reduce the incidence of non-specific conjunctivitis.
3. That the antibiotics used in controlled studies apparently were as effective in preventing gonorrheal ophthalmia as was silver nitrate; e.g., no cases were reported in either group.

In 1955, the Committee was concerned with the possible occurrence of sensitization to locally administered antibiotics, the possible emergence of antibiotic resistant strains of bacteria, and possible difficultes in maintaining stability and potency of antibiotic preparations under hospital storage conditions. Furthermore, the Committee was aware of studies in progress in which no routine prophylaxis was carried out. In view of these considerations the Committee on Fetus and Newborn did not recommend any change in the existing procedure for the prevention of gonorrheal ophthalmia.

On February 8, 1958, the committee on Fetus and Newborn again reviewed the problem in light of additional information:

1. In a large metropolitan hospital, elimination of eye prophylaxis of any type resulted in the occurrence of four cases of gonorrheal ophthalmia within four months. Significantly none of the others had given any evidence of disease, and one of the babies developed conjunctivitis after discharge from the hospital. This hospital had had no cases of

gonorrheal ophthalmia since the institution of silver nitrate prophylaxis.

2. In a study from Australia, babies receiving no prophylaxis demonstrated as high an incidence of discharging eyes as did babies receiving silver nitrate. Furthermore, babies receiving no prophylaxis demonstrated a higher incidence of pathogens on culture (non-gonococcus) than did the babies receiving silver nitrate. The most common organism found in both groups was staphylococcus aureus.
3. Various prophylactic measures were considered in the context of the problem of antibiotic resistant infections in newbo4n nurseries together with the fact that the organisms commonly found in the eyes of newborn infants have very limited sensitivity to currently available antibiotics.

*NEWS LETTER. American Academy of Pediatrics, Vol. 9, No. 3. March, 1958.

On the basis of available evidence the Committee believes:

1. That gonorrheal ophthalmia still constitutes a definite hazard to the newborn infant.
2. That silver nitrate has amply demonstrated its effectiveness as a prophylactic of gonorrheal ophthalmia.
3. That the occurrence of non-specific conjunctivitis does not, of itself, constitute adequate reason for change.
4. That the routine use of antibiotics may introduce further problems referable to control of infections in newborn nurseries.

Therefore, the Committee on Fetus and Newborn recommends that the routine use of 1% silver nitrate for prophylaxis of gonorrheal ophthalmia be continued.

INFECTIOUS DISEASES—NOVA SCOTIA
Reported Summary for the Month of July, 1958

Diseases	NOVA SCOTIA 1958 Cases	1958 Deaths	1957 Cases	1957 Deaths	CANADA 1958 Cases	1957 Cases
Brucellosis	0	0	0	0	0	0
Diarrhoea of Newborn	0	0	0	0	0	0
Diphtheria	0	0	0	0	2	0
Encephalomyelitis—Infectious	0	0	0	0	1	3
Food Poisoning	0	0	0	0	0	0
Gastroenteritis (1) Infectious	117	0	43	2	81	24
Hepatitis—Infectious Including Serum Hepatitis	44	0	3	0	0	0
Impetigo of Newborn	0	0	0	0	0	0
Influenza (if unusual number of cases)	605	0	50	1	724	154
Meningococcal Meningitis and Meningococcemia	0	0	0	0	15	12
Pertussis	232	0	31	0	514	448
Poliomyelitis (paralytic (non-paralytic	0 0	0 0	0 0	0 0	5 1	21 11
Scarlet Fever and Streptococcal Sore Throat	74	0	89	0	345	297
Tuberculosis (pulmonary non-pulmonary	17 4	0 0	4 0	0 0	370 45	545 49
Typhoid and Paratyphoid Fever	1	0	0	0	8	21
Venereal Disease (syphilis) (gonorrhoea)	5 6	1 0	5 54	0 0	150 1004	154 1083
Anthrax	0	0	0	0	0	0
Cholera	0	0	0	0	0	0
Psittacosis	0	0	0	0	0	0
Rabies	0	0	0	0	0	0
Smallpox	0	0	0	0	0	0
Tetanus	0	0	0	0	0	0
Trichinosis	0	0	0	0	0	0
Tularemia	0	0	0	0	0	0
Other rare diseases	0	0	0	0	0	0
Other (if unusual number of cases)	0	0	0	0	0	0

(1) amoebic and bacillary dysentery and salmonellosis

Remarks: Delayed reports for the month of June showed that there were two infant deaths from gastroenteritis, one infant death from meningococcal meningitis, and two deaths in adults from influenza. One of the tuberculosis deaths during the month of July was from tuberculous meningitis.

FREE TREATMENT OF POLIOMYELITIS

Since April 1, 1956, the Department of Public Health has provided for free treatment of poliomyelitis cases in the poliomyelitis clinics in Nova Scotia, after the first thirty days of treatment in such clinics. With improved methods of diagnosis, we are now finding that cases of illness which formerly would have been called poliomyelitis are not caused by the poliomyelitis virus. Three such cases are known to exist in the Province at the present time. Since such cases are clinically identical with poliomyelitis and require the same kind of treatment, the Department of Public Health has seen fit to include them in the poliomyelitis free treatment program. Accordingly, an additional paragraph has been added to the Statement of Policy with respect to the Free Treatment of Poliomyelitis at the Provincial Poliomyelitis Clinics. The new statement of policy is as follows:

RE-STATEMENT OF POLICY WITH RESPECT TO FREE TREATMENT OF POLIOMYELITIS AND OTHER PATIENTS AT THE PROVINCIAL POLIOMYELITIS CLINICS

July 1, 1958

1. As of April 1, 1956, it has been the policy of the Department of Public Health to pay for treatment of poliomyelitis patients at the Provincial Poliomyelitis Clinics.

2. These clinics are located at the Victoria General Hospital, Halifax; Sydney City Hospital, Sydney; St. Martha's Hospital, Antigonish; and the Yarmouth General Hospital, Yarmouth.

3. Regular admission policies of the hospital concerned will apply in each of these clinics.

4. The Department will not pay for cases of poliomyelitis from outside the Province.

5. The Department will not pay for the first thirty days treatment of poliomyelitis in the Provincial Poliomyelitis Clinics. The Department will pay for hospital treatment **subsequent to the first thirty days** and there will be no charge to the patient for this treatment.

6. With regard to chronic cases having no previous admission, these will be dealt with in the same way as acute cases, that is, the Department will pay for all treatment subsequent to the first thirty days in the Clinic.

7. Since the patient becomes a charge of the Department of Public Health after the first thirty days in hospital, the hospital must report to the D.M.H.O. on form C.D.C. 3 (attached) as soon as laboratory reports have been received.

8. C.S.F. and stool specimens, accompanied by clinical history, must be sent to the Virus Laboratory at Halifax as soon as possible after admission,

if the patient is to be eligible for free treatment after the initial thirty days in hospital or clinic.

9. At the end of the first thirty days' treatment, application must be made to the D.M.H.O. giving reasons why future treatment will be required at the expense of the Department of Public Health. The D.M.H.O. must approve the application before forwarding it to the Central Office in Halifax.

10. With regard to poliomyelitis cases who are residents of the City of Halifax, reports and applications for free treatment will be sent to Dr. A. R. Morton, Commissioner of Health and Welfare.

11. With improved methods of diagnosis, we are now finding that cases which formerly would have been called poliomyelitis are not caused by the poliomyelitis virus. These cases are clinically identical with paralytic poliomyelitis and require the same treatment. As of July 1, 1958, therefore, this policy is modified to cover the following:

A febrile, or prodromal illness, followed by motor paralysis of one or more limbs or respiratory muscles, lasting thirty days or longer, with or without sensory disturbance. Such cases must be accompanied by complete cytological and biochemical examination of the C.S.F., also by virological examination of stools and C S.F. To be eligible for benefit, the case should require treatment, and be admitted to one of the above mentioned poliomyelitis clinics.

Massive Haemorrhage Into an Adrenal Pheochromocytoma*

Irreversible shock and sudden death due to massive unilateral adrenal haemorrhage without sepsis is an unique, often unrecognized syndrome, death usually being ascribed to some other catastrophic illness. The case reported here illustrates the diagnostic difficulties that may be encountered. In this case it was established at autopsy that there was a haemorrhage into a previously unsuspected pheochromocytoma. It is concluded that a high index of suspicion is necessary for the correct diagnosis of a case of acute collapse and pulmonary oedema occurring with unilateral adrenal apoplexy. This type of case is regarded as a definite clinical syndrome that may prove to be remediable if early diagnosis is made and treatment instituted.

*Lehman, D. J., and Rosof, J., New England Journal of Medicine. 254: 1957. Medical Abstracts. August, 1957.

Secretary's Page

Annual Meeting — The Medical Society of Nova Scotia

The dates are October 24th (Friday) and October 25th (Saturday). As previously announced this is primarily a business meeting because of The Canadian Medical Association meeting in Halifax in June.

It will follow immediately on the Annual Refresher Course which is Monday, October 20th to Thursday, October 23rd, inclusive.

The place is the Lord Nelson Hotel, Halifax.

The programme will include a panel discussion on Hospital Insurance chaired by Doctor D. M. MacRae. The President's reception, banquet and dance will be held Friday evening. Members are requested to make their own hotel reservations as there is not a Housing Committee this year.

Make your plans now to attend the Annual Meeting and the Refresher Course.

Group Life Insurance

The Executive Committee at the June meeting approved the proposed plan to increase this policy from $5,000 with $2,000 bonus to $10,000 with $1,000 bonus at a moderate increase in premium. The proposed plan will be effective if 75 per cent of those participating indicate approval for the change.

A letter was sent to participating physicians on July 23rd which provided the information and had a form which was to be detached and forwarded to the Executive Secretary. The response was reasonably good, but because of the holiday season, a follow up letter was sent on September 9th to those participating physicians who had not replied. Further replies are arriving daily. However, it is desirable that all should indicate their wishes in this matter which appears to be so worthwhile. Have you sent in your reply? If not, please do so.

Hospitalization Plan

There is every indication that the Hospital Insurance Plan for Nova Scotia will come into effect on January 1st of 1959. An important objective is to have the medical profession and the public made aware of facts relative to the hospitalization under the plan to be put into operation. To this end, two booklets, of the question and answer type, are being prepared by the Hospital Service Planning Commission for distribution; one to the public and the other to the medical profession.

A representative of the Hospital Service Planning Commission has met with members of the Advisory Committee (nucleus) on Health Insurance and the Chairman of the Committee on Public Relations prior to preparation of the booklets. Another meeting will take place.

It is planned to have the brochure for the profession in the mail a week or so prior to that for the public, so that the members of the profession will be better prepared for discussion with their patients and others. It is expected the booklets will be mailed during October.

The National Hospitalization plan, in which the Federal and Dominion governments share the cost of hospitalization and certain diagnostic services has been endorsed by The Canadian Medical Association and its Divisions. While there will be variations in details in each of the provinces, the general orinciples apply to all.

The Medical Society of Nova Scotia, through its Advisory Committee on Health Insurance, is enjoying close liaison with both the Hospital Service Planning Commission and an Advisory Committee of the Nova Scotia Section of the Maritime Hospital Association. A comprehensive report will be presented at the Annual Meeting.

In the meantime the brochure, presently in preparation, should do much toward an explanation of the plan.

C.J.W.B.

WANTED:

GENERAL PRACTITIONER

Recent Graduate for well-established group practice in Dartmouth. Excellent opportunity for wide experience and good advancement. Apply to Nova Scotia Medical Bulletin office.

APOLOGY

Due to a typographical error we regret that Neonatal Intestinal Obstruction by Edwin F. Ross, M.D., F.R.C.S., (C) did not appear in the Table of Contents of the August issue, and the article by G. J. LeBrun, M.D. and F. G. Dolan, M.D., Treatment of Compound Fractures which appeared in the Table of Contents will be printed in a future issue.

Personal Interest Notes

Dr. Richard L. deC.H. Saunders, head of the Department of Anatomy of Dalhousie University, has been granted a James Picker Foundation award. This was announced by the National Research Council of Canada which is administering the Foundation's Canadian funds for the first time. The grant will be applied to fostering study presently being done by the Professor in patterns of highly vascularized active tissue as are found in the brain.

Dr. Saunders possesses an X-ray microscope which provides great penetration and magnification and a wide field of view which makes it more valuable than standard radiographic methods.

Born in South Africa, and educated at Rhodes University, S.A., and Edinburgh University, Scotland, Dr. Saunders was made head of the Department of Anatomy at Dalhousie University in 1950.

DALHOUSIE REFRESHER COURSE

The following information regarding this year's course will be of interest:

(1) The Guest speaker in Surgery is B. K. Rank, C.M.G., M.S. (Melb.), F.R.C.S., F.R.A.C.S., Professor of Surgery at the University of Melbourne.

(2) The College of General Practice will participate in the form of a round table "The more common infectious diseases in general practice."

(3) Medical motion pictures will include "Acute Abdominal problems" and "Three Key Questions in Coronary Disease."

Treatment of Anxiety States With Meprobamate*

Meprobamate was administered to 312 patients treated at the Psychiatric Department of Albany Hospital. It showed definite effectiveness in psychoneurotic anxiety states, and it appeared to have a selective action in conditions in which anxiety and tension were prominent factors.

The combination of meprobamate with sodium amytal in certain cases seemed to be of greater value than either drug given alone. A few patients reported drowsiness or dizziness, but the former subsided spontaneously upon continued administration. Three patients developed mild skin rashes. Other side effects were not reported. While meprobamate appears at least as effective as other tranquilizers, it seems to be safer and better tolerated and has the added advantage that it does not affect the autonomic functions of the body.

During recent years a number of excellent drugs have become available for the treatment of the emotionally disturbed. With the exception of meprobamate, those most widely used are either antihistamines or *Rauwolfia* compounds. Both these groups appear to act primarily on the hypothalamic area of the brain, with resultant powerful effects on the autonomic functions.

Chemically, meprobamate is entirely different from either of these two major families of tranquilizing drugs. It exerts its action primarily on the thalamus rather than on the hypothalamus. Therefore it is able to produce therapeutic results without distributing the delicately adjusted autonomic equilibrium of the body.

This fact is of special importance in treating outpatients who must carry on with their every day work and activities, and in whom such autonomic side reactions as stuffy nose and diarrhoea may be very disturbing. Of even greater importance in outpatient treatment is the low toxicity of meprobamate. While the incidence of agranulocytosis, jaundice, parkinsonism, and depression resulting from the antihistamine and *Rauwolfia* tranquilizers may not be unreasonably high in relation to the total number of patients treated with them, still the possibility of their occurrence makes necessary a constant vigilance that is usually not feasible in outpatient practice. With meprobamate, transient drowsiness and an occasional skin reaction are the worst that can be expected. Therefore meprobamate therapy would seem to be the treatment of choice for this type of patient.

*Osinski, W. A., Annals of the New York Academy of Sciences. 67: 1957. Medical Abstracts, August, 1957.

Use of Meprobamate in the Treatment of Skeletal Muscle Spasm*

Meprobamate was administered to 107 patients with symptoms of muscle spasm, limitation of motion, pain and tenderness, and shift of trunk. It was found to be the best muscle relaxant available to date for use in these conditions. Significant relief was provided to nearly all patients, and particularly to those suffering from acute back strain and acute cervical myositis. Two patients with idiosyncrasies to the drug developed skin rashes. No other toxic reactions were observed. Meprobamate is fully effective on oral administration, is long-acting, and does not produce gastric disturbances or other undesirable results.

*Eisenberg, A. H., and Deviaser, J. A., Annals of the New York Academy of Sciences. 67: May, 1957. Medical Abstracts, August, 1957.