CHAPTER 14

THERAPEUTIC APPROACH

BIOLOGICALLY GUIDED THERAPY

THE STUDIES PREVIOUSLY DESCRIBED have identified many factors involved in the pathogenesis of abnormal conditions and have shown that there are similar factors which also govern the pharmacological activity of various agents. Out of this peculiar relationship between abnormal conditions and agents has evolved a therapeutic method which is fundamentally different from methods in common use.

In conventional therapeutic efforts against disease—in chemotherapy of cancer for example—methods as standardized as possible are sought. The goal is to find agents capable of influencing the cancer cells, if not in all tumors, then at least in tumors of the same origin. Within the limitations imposed by the general toxicity of the agent, the conduct of treatment is standardized as far as possible. The criterion of value of a treatment is its ability to overcome individual variations.

In our approach, in clear contradistinction, the effort is to influence the complex condition as it is present at different levels of the organization. It corresponds to treatment individualized as far as possible. Therapeutic efforts are guided in all their aspects—choice of agents, doses to be used—by existing manifestations with their multiple quantitative and qualitative variations. The fact that many of these variations occur during treatment, as a response of the organism induced by the medication itself, increases the individual character of treatment. No prediction can be made about the whole course of treatment to be used for an individual patient because the individual qualitative and quantitative changes which occur during the treatment cannot be foreseen.

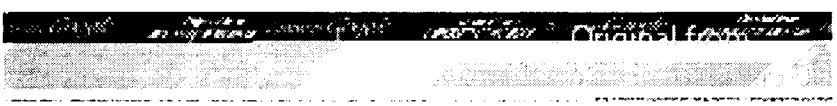
In this approach to therapy, the patterns of manifestations constitute the criteria which determine the choice of the group of agents, the specific members of the group, and the dosages to be used. Throughout, clinical and analytical manifestations are the major factors that guide treatment. The clear systematization of the relationship between analytical findings and therapeutic indications is vital.

The fundamental offbalances, their patterns and deviations, thus guide the therapeutic approach. The nature of the fundamental offbalance, in general, indicates which of the two basic groups of agents is to be used; the patterns show which substances from these groups are desirable; while the quantitative changes in these patterns, especially under the influence of the agents, determine the doses to be administered. Any change in biological manifestations is followed by change in therapy. We call this *biologically guided therapy.*

Through the years, although this biologically guided treatment has remained fundamentally unchanged as an approach itself, applications have evolved. Efforts have been made to find increasingly precise criteria and more efficient agents.

Each of the basic physiopathological concepts has greatly helped to develop standards for the guidance of treatment. For instance, the concept of organized conditions has led to the concomitant use of several agents from the same group instead of just one. The idea for this was derived from the fact that the concomitant manifestations at different levels show relative independence; they must be influenced separately. The concept of physiopathological dualism has indicated the need to use, according to the offbalance present, agents from one or the other of the two groups with antagonistic properties. The role of the lipids in dualism has underscored the importance of these substances as active agents able to induce fundamental changes. The dualism of other constituents has been the basis for their use. The mechanism of natural defense has shown the advantage of using two systems simulating, in part, the kind of dualistic response which occurs naturally. As more has been learned about these basic concepts, the therapeutic approach, while it has remained fundamentally the same, has evolved and become increasingly effective.

The value of biologically guided chemotherapy appears clear when we compare the effects obtained by using agents with and without the guidance furnished by this method. Several patients treated at another center of research with a well-known agent, such as a nitrogen mustard gas derivative, have been studied. Analytical data showing the patterns present in these patients were obtained but were not used to influence the conduct



of treatment. Favorable results were seen in a few of these cases—when, by happy accident, the treatment applied was suitable both to the original problem and to the changes occurring during treatment, as revealed by analyses. In the failures, there was no such fortunate coincidence. The fundamental offbalance present called for an agent other than what was used. Or changes occurring during treatment indicated that use of the agent should be discontinued, although this was not done.

We have employed the same agents in some patients but with treatment guided by individual manifestations. In some cases, the analyses indicated the need not only for more prolonged treatment, but even for the use of dosages higher than those usually accepted. In others, on the contrary, they indicated the need to reduce dosage or even to stop the treatment, although the doses were, according to the usual posology, too small. It is interesting to note that in some cases, the treatment has been stopped and restarted several times on the basis of analyses. The clinical results—immediate and long-range—were definitely better than in patients given unguided therapy.

In analyzing the development of clinical applications of this form of biologically guided chemotherapy, progress can be seen to have resulted as knowledge has increased in three areas: criteria, agents used, and method of application.

Criteria

We have discussed the different symptoms and analytical changes with dualistic character encountered in pathological conditions. At various stages, all were considered as potential criteria for guided therapy. The value attributed to them as indications for treatment has changed as research has progressed. Some of the analytical tests have been found to reflect changes limited to a special level, while others of more general value have been found to furnish indications of broader offbalances themselves. The importance of some criteria was established only after many years. Others, once considered of major usefulness, have appeared to be less reliable as time went on. Body temperature, for example, in spite of the frank dualistic aspect often seen, has been considered for a long time to be influenced by too many factors to furnish any valuable information. With the development of our research, however, temperature has become an important criterion for administration of agents but limited toward manifestations at the level of the organism.

Urinary specific gravity and pH; excretion of chlorides, sodium, calcium and sulfhydryl; total blood and serum potassium; and the count of eosinophiles in circulating blood—all have been used individually with the

hope that they would indicate the type of fundamental offbalance present, and consequently, which group of agents should be used. Recently, however, we have come to use these measurements rather as criteria of changes at different levels. Urinary surface tension has thus become important as an indication of the offbalance at the levels above the cells while potassium in blood indicates the offbalance at the level of the cells. Years of investigation have shown conclusively that proper criteria represent the principal condition for success in treatment by guided chemotherapy.

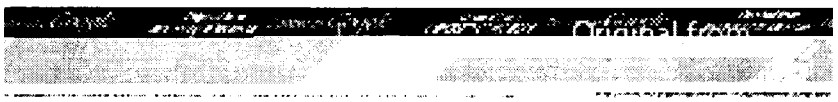
The Agents

The relative independence of the various levels involved in a condition like cancer, which originates below the level of the nuclei and progressively involves higher levels as it evolves until it terminates as a systemic condition, necessitates having several agents chosen specifically for their ability to work at these different levels.

Over the years, we have utilized many agents. The level at which they are most active, the nature of activity from the point of view of dualistic intervention, and integration of activity in the frame of the defense mechanism, represent the factors which determine the specific use of these agents. It must be emphasized that, in the study of pharmacodynamic activity, the value of information furnished by tests in laboratory animals is limited. Because changes in patterns in animals cannot be followed, we have been obliged to follow such changes in humans.

Method of Application

The critical role played by each level of organization in a complex condition—and the independence of these levels—underscores the urgency of applying therapeutic agents capable of acting at specific levels where they are needed. Such applications have been made possible through special affinities of various agents for different levels. Their structure—and especially their content of specific elements which belong to specific levels—account for their tendency to act at specific levels. However, it has often been judged necessary to insure intervention of an agent at a given level by applying it directly at the level itself. The injection of an agent into a tumor or into a region of the body, through surgical chemotherapy, represents one type of procedure insuring level activity. Another procedure has been to inject an agent prepared in vitro so that it is bound to specific body constituents, such as cells or nuclei. In the latter procedure, the specific defense mechanism is seen to take place at the level of the body constituent and thus desired level activity is obtained.



In the development of this research, we faced another problem which is basic to all therapeutic attempts but especially important in cancer: evaluation of the results obtained.

Evaluation

Incontestably, favorable results have been obtained in cancer with many agents. However, because of the variety of manifestations, evaluation of the changes obtained has been the subject of much controversy. Each clinical worker in cancer has his own ideas about the importance of various changes obtained and often utilizes as criterion changes less accepted by other workers. A systematization of evaluating standards appeared necessary and it seems possible to do so under the concept of the disease as an organized complex condition.

In the minds of most workers in the field of cancer today, any therapeutic procedure aimed at the control of cancer must prove itself in tumors in animals. We have already mentioned the reason why control of human and animal tumors represent two different problems. Failure to recognize that the results obtained in animal cancer do not necessarily apply at all in human cancer has led to failure of the tremendous project of screening virtually all known substances for their effects upon grafted animal tumors.

The unguided treatment of cancer in animals, as carried on today, *i.e.*, without any consideration of existing offbalances, seems to explain the limited importance placed upon many changes obtained in these experiments. But even if evaluation is confined solely to the influence exerted upon the cancerous cells in unguided treatment, the same agent can appear active or inactive, depending mainly on coincidental circumstances. Its influence may change from favorable to unfavorable during, and due to, the treatment. Because of this, it is quite probable that many useful agents are not being recognized in the simple screening method used today. Most of the agents which we have found incontestably valuable in guided therapy appeared to be entirely ineffective when used in unguided treatments on small animals. As long as not enough valuable criteria are available to permit guided therapy in experiments in animals, the results would have only a relative value: to furnish useful information about limited problems such as toxicity, special pharmacodynamic activity, etc.

Under the concept of cancer as a complex condition, all manifestations, not just those directly related to the anatomical presence of cancerous tumors, must be regarded as important.

The tendency of almost all cancer workers is to limit evaluation exclusively to changes observed in tumors. Without underestimating in any

way the importance of these changes, we must emphasize the importance of other manifestations. For a subject in the systemic terminal phase, any change obtained in the tumor will have little immediate importance, whereas a beneficial change in systemic metabolic anomalies will be of great immediate value. Similarly, for a subject in the invasive or painful phase, any influence exerted upon the organic or systemic functions will be of less immediate importance than a beneficial influence upon pain or upon the cancerous lesion. With cancer recognized as a complex condition, the decision of many scientists, especially clinicians, to limit evaluation to changes only in the tumors would appear to be unilateral and unrealistic.

We tried to systematize evalution of results obtained in cancer treatment by considering all the manifestations present in the patient and by assigning to each its relative value. In addition to any decrease or disappearance of tumor masses, various analytical changes, improvement in general well-being, gain in weight and control of pain represent accomplishments, the importance of which depends on the severity of these manifestations in the individual case.

With all these factors in mind, we have evaluated the various results obtained through biologically guided treatment over a period of many years, relating them to agents and criteria which were changed, of course, as research progressed.

The study of different complex conditions has emphasized the fact that many of the manifestations present are common to different diseases. Through the variety of pathological manifestations present in these conditions, we had the opportunity to study many problems specific for these conditions or of general interest. The therapeutic method consequently has been applied in many noncancerous conditions. Before presenting an analysis of the progress of this research in the field of cancer, it may be of interest to review results of the same therapeutic approach in other conditions, each with its specific problems.

THERAPEUTIC APPLICATIONS IN CONDITIONS OTHER THAN CANCER

From the beginning of this study, manifestations, clinical and analytical, present in a variety of abnormal conditions, have appeared to conform to the basic physiopathological concepts presented above. In these varied conditions, however, more often than in advanced cancer, some analyses have shown no abnormal patterns while others have shown them so constantly as to indicate that certain anomalies, often limited to specific levels of or-

ganization, are of great importance. In spite of individual variations, some of the conditions studied have shown patterns and interrelationships of patterns that provide characteristic analytic pictures which will be analyzed in further publications. Furthermore, some of these patterns appear to be so strongly related to a given condition that our attention was directed to the idea of a fundamental relationship between the processes related to the patterns and the pathogenesis of the condition itself. The following examples illustrate this.

An impressive relationship was found between the presence of peroxides in urine and schizophrenia. We mentioned previously the reaction which we devised for detection of these substances in urine. This reaction would indicate the existence in the body of abnormal processes in oxygen metabolism, leading to the appearance of peroxides in the urine. We saw that these processes ultimately could be related to an abnormal intervention of fatty acids, corresponding to the oxygen phase of offbalance D.

Daily urinary analytical patterns were studied in a group of 27 advanced schizophrenics over a period of three years. Over 27,000 urinary samples were examined and more than 135,000 tests performed. Oxidizing substances were found in 87% of these samples. This appears to be highly significant when compared with only 2% positive values in subjects considered clinically normal, and 4% in cancerous cases submitted to various treatments. Not a single negative analysis was seen in some of these schizophrenics during the three years of daily testing. This suggested that the metabolic abnormality, characterized by the appearance of peroxides, might play an important pathogenic role in this disease. (221)

Another example of a pattern revealing characteristic pathogenic processes was seen in geriatric cases. Old people often have a manifest abnormality in urinary S. T. Figure 261, page 648 shows the values encountered in old people compared to those in subjects of mixed ages. The high surface tension in the aged group is related to predominance of sterols at the systemic level. Such predominance is also found at the organic level of the skin, for instance. A clinical test, wheal resorption time, indicated abnormal values for almost all the aged subjects studied, as shown in Figure 68. These data, integrated into the general concept of complex conditions, led us to the pathogenic concept of old age presented above.

The urinary chloride retention index in subjects in a state of shock consistently shows such exceptionally high values that our attention was directed to the study of the role of abnormal metabolism of chlorides in the pathogenesis of the condition itself. This view has been confirmed by further research, as mentioned previously.

The study of the different conditions in terms of fundamental pathogenic concepts has had other consequences. It has established clearer relationships between these conditions and cancer than previously recognized. In fact, many of the data first obtained in the studies of these other conditions have been applied specifically to cancer.

One example is shock. Occurring in the terminal stage and usually leading to death, shock often has been considered to be one of the "complications" of advanced cancer. Under the concept of organized complex condition, however, it could be seen that, in cancer, shock is related to offbalance type D of the terminal systemic phase. The study of shock has greatly contributed to the knowledge of this offbalance in cancer.

The therapeutic approach, in which the choice of agents and the doses used are determined by the different patterns present, has been useful in many noncancerous conditions in which the anomaly apparently is limited to one level of organization or even to a special group of entities. As examples here, we will discuss conditions in which manifestations are produced by an acid-base tissular abnormality.

ABNORMAL LOCAL ACID-BASE MANIFESTATIONS

Pain, itching, vertigo and dyspnea are symptoms of many conditions often far apart etiologically. We have seen that, according to our research, these symptoms are related to an acid-base abnormality at the tissue level. The ideal treatment would be to remove the cause of the symptom, to act upon the etiological factor. This ideal treatment would be entirely different if the symptom stems from a systemic toxic condition, a cancerous lesion, a local inflammatory process or a local allergy, for example. But the great variety of causes that can induce such symptoms as vertigo, pain, itching and dyspnea, often makes this ideal therapy almost impossible, particularly in everyday medical practice.

Another approach to controlling these symptoms would be one which is not especially concerned with the etiological factors involved but with influencing the specific pathogenic changes underlying each of these symptoms. But as such specific changes have not yet been defined, symptomatic treatment has remained as the only practical recourse in these instances.

Recognition in the physiopathological changes present in pain, itching, vertigo and dyspnea of an acid-base pattern, has permitted another therapeutic approach on a different, more precise basis. These symptoms, with their dual pathogenesis, have been treated according to the two possibilities: acid or alkaline pattern. Identification of the specific pattern, as noted

previously, is simple. Furthermore, pain results from an abnormality present at one level of organization, the tissues. With two groups of antagonistic agents, both capable of acting at the tissular level, the therapeutic problem is reduced to the choice between these agents according to the pattern present. The therapeutic problem—previously so complex because of the need to consider so many possible etiological factors so often unrecognizable—is simplified by this approach to a choice between two groups of agents, determined by one easily identifiable factor.

The means used to recognize the acid-base pattern vary with each symptom. We present here a resume of the research made in this direction.

Pain

We have seen that pain can be sensorial or symptomatic, and that the latter has a dual pathogenesis with an acid or alkaline pattern. Reduced to the problem of an acid or alkaline offbalance occurring at the tissular level, the treatment of pain is greatly simplified.

The first problem was to determine the pattern present. The relationship between variations in the curve of pain intensity and concomitant changes in the urinary pH, previously discussed, has been used for such determinations. The simplified method of comparing two urine samples, one corresponding to a period of pain and the other to one of calm, has proven very useful.

Among other analyses, only changes in serum potassium content have appeared helpful in the recognition of the pain pattern. This can be explained by the fact that most of the other routine analyses do not inform us specifically about changes at the tissue level where pain occurs. A high serum potassium level, increasing during pain exacerbation, indicates an alkaline pattern; a low level, decreasing during pain exacerbation, indicates an acid pattern.

Another, sometimes simpler, technique for recognizing the pattern is the response of pain to administration of acidifying or alkalizing agents, as seen above. Also, some substances, while being used as therapeutic agents, indicate the pattern through the responses they induce. Butanol and sodium thiosulfate in adequate dosages (1 cc. of a 6.5% solution of butanol or 1 cc. of a 4% solution of sodium thiosulfate injected intramuscularly) are examples. The intensity of an acid pattern of pain is increased by butanol, and decreased by thiosulfate. The inverse occurs in pain of an alkaline pattern.

With the pattern of the pain recognized through one of these means, agents are chosen from the two groups, anti-A for acid pattern and anti-D for alkaline. In each group however, some agents have been found to be

more effective than others because of their greater activity at the tissue level. The following agents have been found to be most effective against acid pain, in the order presented: lipoaldehydes and especially propionic aldehyde, sodium thiosulfate, sulfurized tetrahydronaphthalene, the acid lipid fraction of various organs, polyunsaturated fatty acids, epichlorohydrin, and selenium in the form of perselenide. For an alkaline pattern, agents with a positive polar group, such as butanol, nikethamide, insaponifiable fractions, glycerol and heptanol are effective in that order.

Once the agent to be used is chosen, the dose which can vary greatly from case to case, is easily determined from the clinical response. In practice, the patient is given a small dose. If the intensity of the symptom decreases but is not completely controlled, the same dose is usually given three hours later. If the symptom intensity remains the same, the dose is continuously increased more or less rapidly, in accordance with the severity of the symptoms, the medication being repeated this time at intervals varying from a half hour to every three hours.

On the other hand, if the symptom disappears after the first administration of the agent, medication is not repeated until the symptom reappears. If the symptom is controlled for less than six hours by the dose used, the same dose is given when the pain reappears. If more than six hours of relief follow a dose, the next dose is usually reduced in proportion to the period of time the effect lasted. If 24-hour relief occurred, the dose is reduced by half; if relief was of two days' duration, one-quarter of the last dose is given. However, if, with three successive doses of medication, the symptom increases in intensity each time, always during the first half hour after the medication is administered, it is discontinued and the entire group of agents to be used is reconsidered. A new test for the pattern is performed. If the pattern is the same as before, other agents from the same group are tried. However, if the pattern now is opposite to the original pattern, the group of substances has to be changed.

This technique has produced, with few exceptions, excellent pain relief. This approach to pain has been the object of several controlled studies. S. A. Barragan Martinez (183) and E. Stoopen, (184) in the journal "Pasteur," confirmed our conclusions. From Stoopen's publication we quote two characteristic observations in *Note 1*.

An intensive study of head and neck pain was made by B. Welt and published in the American Medical Assn. Journal of Laryngology (185), with the following conclusions:

"Summary and Conclusions

A series of 120 patients having the symptom of pain in the region of the head and neck has been studied.

The symptom of pain has been analyzed according to Revici's concept concerning the alkaline or acid pattern of the painful symptom.

Eleven cases were eliminated because no pattern was identified; 109 cases showed an acid or alkaline pattern. The results showed a satisfactory result in 84% of the vascular headaches, 100% in migraine headaches, and 75% in the neuralgic group. These results indicate a correlation of Revici's concepts and the results achieved. The simplicity of this method is indicated.

Additional data about Revici's views are given. The relationship to homeostasis and the biology of the cell is indicated.

The problem confronting the clinician in treating cases of this type, on account of the many factors involved, is simplified according to Revici's concept of dualism.

Two additional active products are presented, one acid and the other alcoholic. The data here presented concerned the incidence of the control of the acute symptoms while under observation. Further experience with this method will be necessary. As the method stands, it is a practical method of therapy for the control of pain. Recurrences were seen and controlled."

Our method of controlling pain was the subject of a panel discussion at the American Academy of Ophthalmology and Otolaryngology, New York, N. Y., September 21 and 22, 1954, and of an article published by B. Welt and M. Welt in Modern Problems of Ophthalmology. (186) *(Note 2)*

Trauma

A particularly interesting application of the method described above is in the treatment of pain related to traumatic lesions. The study of wounds from the standpoint of the offbalance present has revealed a definite pattern in their evolution. In all wounds, there is an initial period during which the offbalance is always type D, corresponding to a predominance of fatty acids. This can be recognized indirectly by measuring the local pH which shows alkalosis, the chloride content which shows a manifest increase, and by cytological and histological studies which indicate a rapid cellular aging process, with necrosis and sloughing. In uncomplicated wounds, in humans, the painful period usually lasts a few days. The pain in this initial period is of an alkaline pattern.

The constancy of the alkaline pattern in pain in traumatic lesions elimi-

nates need for any tests, thus simplifying therapeutic choice by reducing agents to be used to one group—those with positive character.

As already noted, some of the agents are more effective than others in influencing alkaline pain. Butanol and heptanol are particularly useful in traumatic pain, followed in order of activity by polyunsaturated alcohols, nikethamide and glycerol.

One important application of these findings is in routine treatment of postoperative pain. For surgical wounds, which represent typical traumatic lesions, butanol appears to be especially beneficial. Its use has been the subject of extensive studies by B. Welt (187) in surgery in otorhinolaryn-

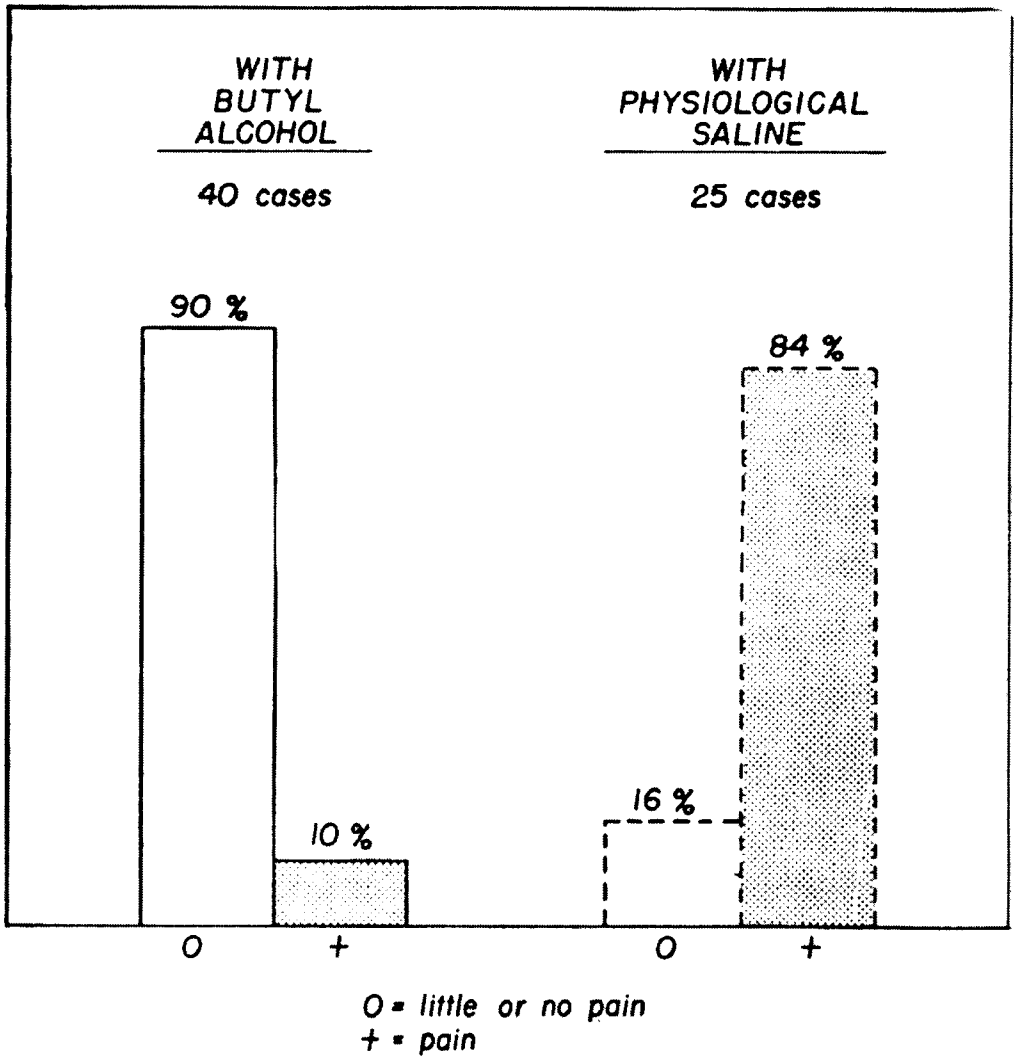


FIG. 144. Results obtained with butanol in postoperative pain—compared with subjects receiving saline as placebo—(From B. Welt—AMA Archives of Otolaryngology. 52. 540, 1950.)

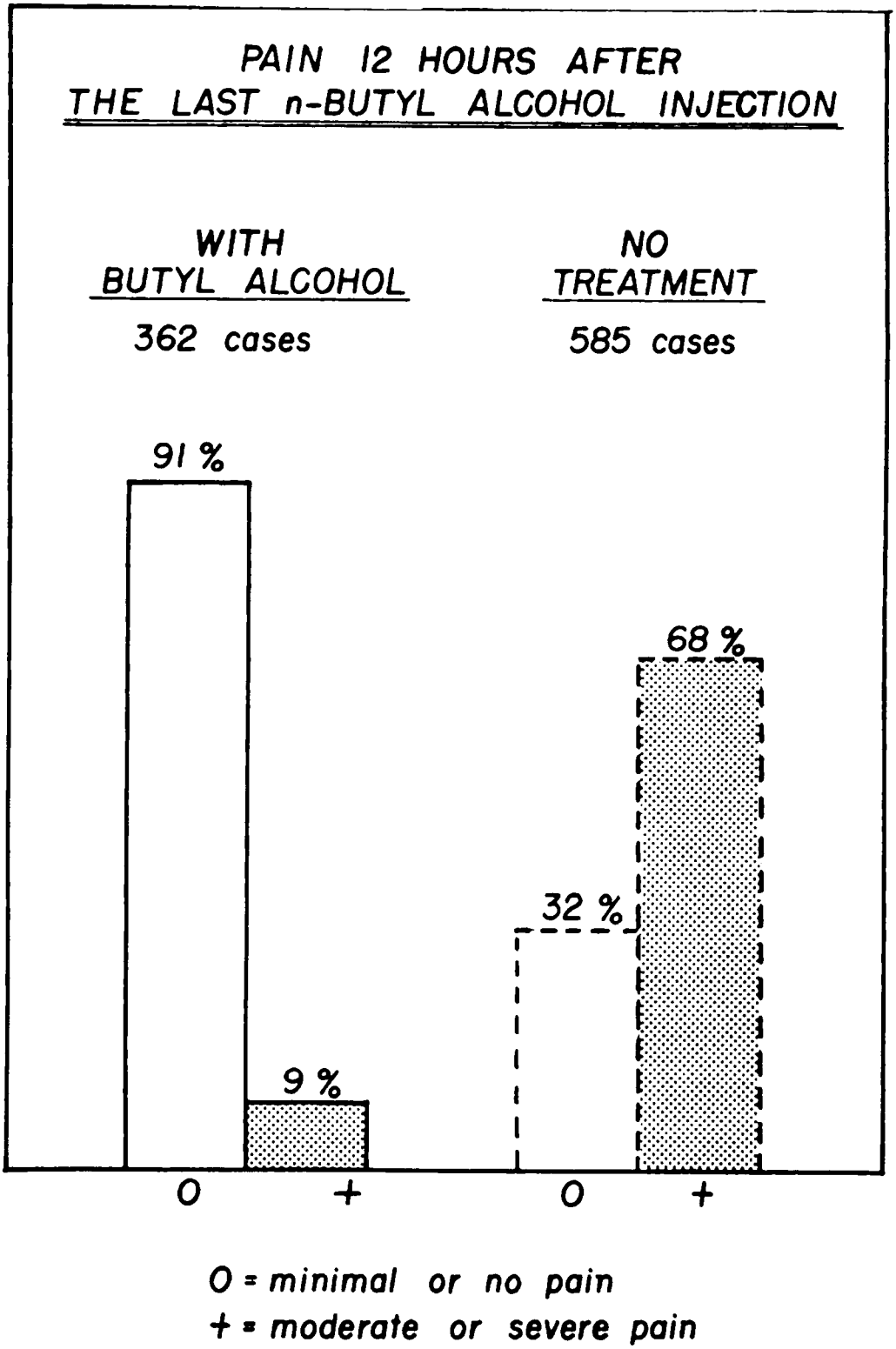


FIG. 145. Results 12 hours after the butanol injections. (From B. Welt, AMA Archives of Otolaryngology, 50, 590, 1950.)

gology, *(Note 2) (Fig. 144)* by M. Welt in ophthalmology (188), by A. Ravich in urology (189) *(Note 3),* and by S. Sheer in plastic surgery. (190)

With more than 10,000 cases treated, butanol seems to be completely safe as well as highly effective. Not a single case of undesirable reaction due to the medication has been noted. The dose necessary to obtain pain relief varies with the amount of traumatized tissue. With an adequate dose of butanol, the patient has a minimum of pain, is conscious, and without impairment of intestinal and bladder function. Butanol also has a marked preventive action against hemorrhage, which will be discussed below.

Success with this medication depends upon adequate dosage. The addition of butanol to the saline solutions customarily used in postoperative care has done much to simplify the problem of administering it in adequate doses without resorting to supplementary injections. Doses as high as 100 cc. or even 200 cc. of 6.5% solution of butanol have been administered in the first days following surgery, with good results and no inconvenience to the patient.

Administered by injection or orally in only very small doses, heptanol is helpful. A mixture of heptanol, butanol and polyunsaturated alcohols constitutes a valuable preparation for controlling postoperative pain. *Butanol, heptanol* and *glycerophosphoric acid* added to *glucose* and *saline* has proved very helpful to control not only pain but also the other disagreeable *post-operative manifestations. (Note 4)*

In other forms of trauma, such as accidental wounds or fractures, the same agents have been equally successful if in sufficient doses.

With their use, the healing period seemed to be shortened, as shown in experiments in rats and rabbits. In animals with standardized wounds, the healing of connective tissue in particular is accelerated. In wounds treated with preparations of cholesterol, sterols or insaponifiable fractions of organs, the healed epithelium shows abnormally high proliferation.

Burns

The pain of burns has been successfully treated with higher alcohols such as butanol, heptanol or polyunsaturated alcohols. However, here the problem is not so simple since pain is only one, and not the most important, of the manifestations. Systemic functions are often so greatly impaired as to represent the immediate cause of death. The higher alcohols are effective in controlling pain and local troubles, while other agents are needed when the condition also involves the systemic level. Glycerol and especially sterols which are present in the insaponifiable fractions of organs such as

placenta, are very helpful in these cases. Anuria of several days' duration has been influenced in several cases, with abundant diuresis occurring only a few hours after the administration of 2-4 cc. of a 10% solution of the insaponifiable fraction of placenta, an effect not obtained with butanol alone, even in large doses. The effect was still more impressive when large doses of butanol, such as 10 cc. of the 6.5% solution every hour, were administered for a few hours before injection of the insaponifiable fraction.

The addition of sodium lactate to butanol in sufficient amount has been seen to favorably influence systemic problems related to burns. Experimentally, we have shown the value of this preparation in extending the survival time of mice.

Under ether anesthesia, adult mice were scalded in water at 90°C for three seconds up to the xyphoid appendix. The survival period for untreated animals was short. Of the various preparations used, the butanol-sodium lactate mixture seemed to be the most active in prolonging survival. *(See Note 13, Chapter 10 and Fig. 138)*

Ultraviolet ray burns, such as occur in sunburn, have been treated with butanol in several hundred cases. We started with 5 cc. of the 6.5% solution orally, and repeated the dose every 10-15 minutes until the painful sensation disappeared. When the burning sensation reappeared, treatment was resumed. It could be seen that butanol not only controlled pain rapidly and completely but also that the skin lesions healed in a shorter time than in untreated subjects.

X-ray and radium burns in animals and humans have responded to the same substances as mentioned above. Standardized ulcerated radiation lesions were inflicted in rats by inserting, between the lips of a skin incision, a needle with radium in platinum or monel metal. A needle with 25 mg. radium in monel metal was kept in place for two hours, one with 10 mg. in platinum for 96 hours. Ulcerations resulted and took four weeks or more to heal. In animals treated with sterol preparations, such as insaponifiable fractions of placenta, wounds healed in much shorter time. Similar effects could be obtained with butanol, although less consistently.

Good results were obtained with the same treatment in radiation burns in humans. In relatively new lesions, pain was relieved after a day or two and rapid healing usually followed. Even in old burns which had not healed for many years, pain was controlled in less than a week and the lesions started to heal. In some of these, scars developed in less than a month.

Vertigo

Another interesting application of the same therapeutic method has been in otological conditions. B. Welt has made a stimulating contribution to the study of ear conditions in terms of the pathogenic mechanism involved and an even more valuable contribution to therapy.

Vertigo was one of the conditions studied. In a few cases, by comparing concomitant variations in the intensity of the symptom and changes in the urinary pH, we had been able to show that acid and alkaline pathogenic patterns exist, similar to those seen in pain.

Going on from there, B. Welt, in an extensive study, has shown the presence of this dualism and has successfully applied the therapeutic method discussed above, to a significant number of cases of vertigo. The major advantage of this method over other treatments for this condition lies in its extreme simplicity.

For vertigo, which has so many different causes, an etiological approach although ideal, has seemed impossible to all workers in the field especially as a routine procedure in medical practice. An initial simplification of the approach could be made by relating vertigo to acid and alkaline patterns, thus reducing treatment choice to two groups of agents. Welt, in a further step, simplified even this procedure, making the method highly applicable in routine medical practice. He administered to patients one or the other of two agents chosen from each group, such as butanol or sodium thiosulfate, being guided in his choice by clinical aspects such as changes in the symptom with the time of day or the intake of food. A favorable change in the symptom was considered to be a confirmation of this tentative diagnosis of the pattern. The treatment was then continued with the same group of agents. An increase in vertigo led to the use of the opposite group of agents. The clinical results obtained by Welt with this simple method are impressive. (190) He arrives at the following conclusions:

"Summary and Conclusions

A series of 44 patients having the symptom of dizziness has been studied.

The symptom of dizziness has been analyzed according to Revici's concept concerning the alkaline or acid pattern of the symptoms.

In 80% of the analyzed cases, the responses have shown the existence of an alkaline or an acid pattern; 12% showed an inconsistent relationship; 8% showed no result.

A therapeutic approach has been devised which corresponds to the presented results.

The control of the symptom of dizziness by this therapeutic approach has been obtained in 80% of the cases.

As compared with other methods of treatment, which are prolonged and involved, Revici's approach is simple in application and effective in its results.

This therapeutic approach based on the dualistic pattern of the physiopathology of the pathological tissues is especially applicable to the symptom of vertigo, which because of the multiplicity of the etiologic and pathogenic factors make a direct medical attack almost impossible.

The evidence presented in this communication relates to the control of the acute attacks of vertigo. Recurrences were observed in this series and successfully controlled.

In the cases submitted in this communication and in subsequent cases subjected to this form of therapy, further observation by this method will indicate whether or not the lesion is permanently controlled."

Welt completed his vertigo study by using many other members of the same groups of agents as they were studied by us for other conditions. The following conclusions appear in Welt's second publication on vertigo. (191)

"*Summary and Conclusions*

A series of 106 cases with the symptom of vertigo has been presented in this and a previous paper and analyzed according to Revici's concept of a metabolic imbalance which exists in pathological foci and manifests itself as a local alkalosis or acidosis.

Seven cases were eliminated for lack of data. This left a total of 99 case studies. This figure represents the sum of 42 cases termed the 1953 series and the present series of 57 cases. The two series were combined and analyzed according to sex, alkaline or acid character of the symptom, and clinical diagnosis.

The analysis showed an average good result of 80% for both series. This percentage indicates a consistent correlation of the use of Revici's method and substances with the results achieved. Additional substances from various sources were utilized in the present study. It is here again emphasized that I have submitted this article for the practical reason that the method described is simple and has been successful in its application. In addition, it gives a new systematization to clinical data in the field of otolaryngology. Finally, this communication points to a vast group of sub-

stances from widely differing sources and of different structures which have similar biochemical activities. The substances presented here are but a few, but they open a pathway for the development of other substances having similar biochemical activities. It is to be hoped that these too, may have a practical application in the field of otolaryngology.

Views on cell permeability and their relationship to fatty acids and sterols are added.

The role of foci of infection and psychological aspects in their relationship to the symptom of vertigo is amplified.

The simplicity of this method of therapy is emphasized, and its integration with a new method of systematization of clinical knowledge is indicated."

Hearing Impairment

Deafness remains the most important problem in otology despite good results recently obtained with surgical procedures such as fenestration and stapes mobilization. Since deafness results from long evolving processes, a logical approach to the problem would be not to wait for the advanced stage where surgery must be used but to try to control the processes before they reach this ultimate state which usually corresponds to sclerosis. Studies of the morphological changes related to progressive deafness have been too limited to present a basis for a biological or biochemical therapeutic approach that would have a chance of success. The nature of the lesions, their minuscule dimensions, and their chronic evolution, offer no opportunity for direct information. Consequently, we tried to adapt to this situation the knowledge acquired through research in the field of abnormal processes in general.

Just as for pain, it was observed that some patients with hearing impairment are aware of differences in their acoustic acuity according to the time of day, *i.e.* some hear better in the morning, some in the evening. There seemed also to be a correlation with the intake of food. Based on these observations, cases of various degrees of surdity were investigated for relationship to acid-base changes. Some subjects showed audiometric variations under the influence of acidifying or alkalizing agents, while others did not respond. When two antagonistic agents were used in the same subject and hearing acuity was analyzed, the changes occurred in two opposite directions. We could interpret this only by analogy to changes in pain and other acid-base symptoms. Accordingly, we postulated that in some cases no activity is going on in the lesions since no changes are induced in the

audiogram by administration of acidifying or alkalizing agents; in others, there is activity which is acid or alkaline in pattern.

Thus, the existence of a response was considered to indicate a still active lesion. Time is not the determining factor. Even in relatively recent lesions, biological activity may have ceased while in other cases, even with very advanced hearing impairment, lesions can still be evolving, with processes not yet advanced to the sclerotic scar phase. This aspect has been extensively studied because of the therapeutic implications, since only an evolving state could possibly be influenced by this method of therapy.

The influence of agents used in other conditions with acid-base pathogenesis was studied in cases of impaired hearing. The first attempt made years ago, with fatty acids and sterol preparations, was not successful. Much better results have been obtained with more recently developed synthetic agents. In the last five years, Welt has devoted much time and effort to this research. He has made thousands of complete audiograms and has used a series of active agents with placebos for control. (192) Welt has studied approximately 460 cases to date. *(Note 5)* In the simplified form, an agent from one or the other group was used for a short time and improvement in the audiogram was taken to indicate that a suspected pattern, acid or alkaline, was actually present.

Clinical results have largely confirmed theoretical views. Regardless of degree of impairment, improvement ranged from nil or almost nil in cases with no more signs of activity, to good and excellent in those with still active lesions. In young patients in whom the proportion of active lesions is high, results were particularly impressive. Hearing impairments of 60-70 decibels or more have been overcome, sometimes in only a few weeks of treatment. These results have been observed to persist in many cases, some thus far for more than three years. However, a tendency for impairments to recur, usually following rhino-pharyngeal infections, has been noted. Generally, renewed treatment has been able to restore hearing to previous values in a short time. *(Figs. 146 to 150)*

It appears superfluous to emphasize here the importance of this contribution to the medical and social problem of deafness. It represents the first approach to treat successfully the pathological processes related to impaired hearing before they lead to advanced lesions which can no longer be influenced except by surgery. Every case of incipient or even advanced hearing loss should be investigated by the simple technique devised by Welt to see if correction by this method is still possible. Surgical intervention should be reserved principally for patients with lesions which correspond to sequels and who no longer respond to biochemical treatment. But even

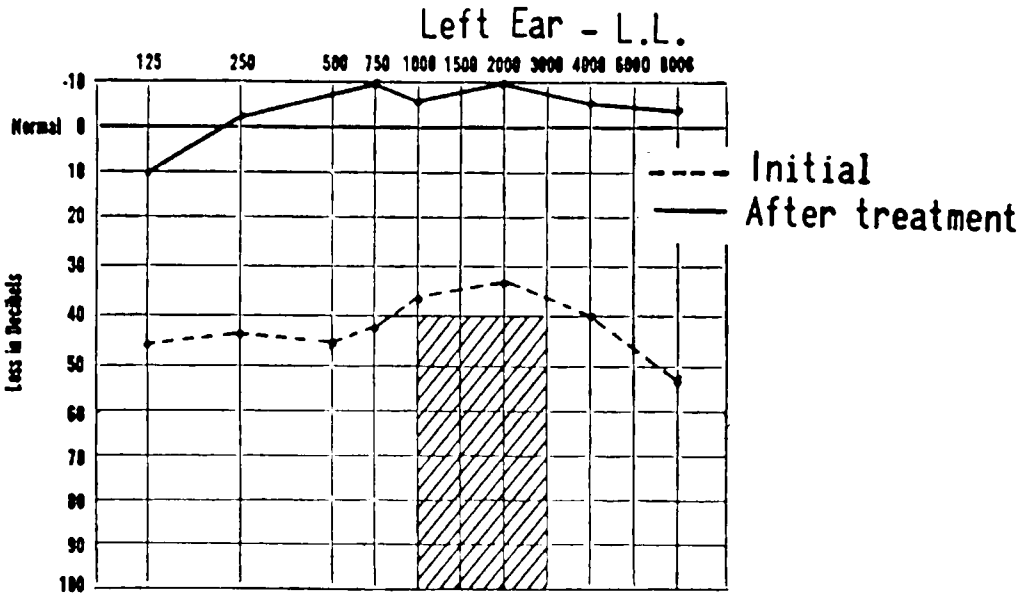


FIG. 146. Manifest improvement in the impaired hearing is obtained in a subject with acid pattern, through guided treatment with negative lipoids. (Courtesy of Dr. B. Welt.)

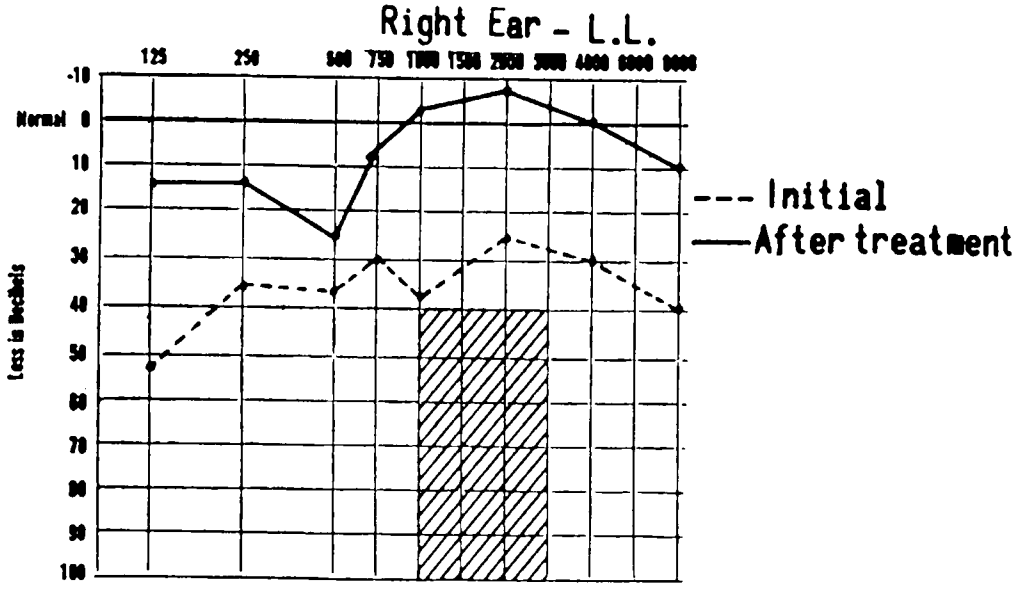


FIG. 146bis. In the same patient as in Fig. 146 the improvement is not as manifest for the right ear as for the left ear.

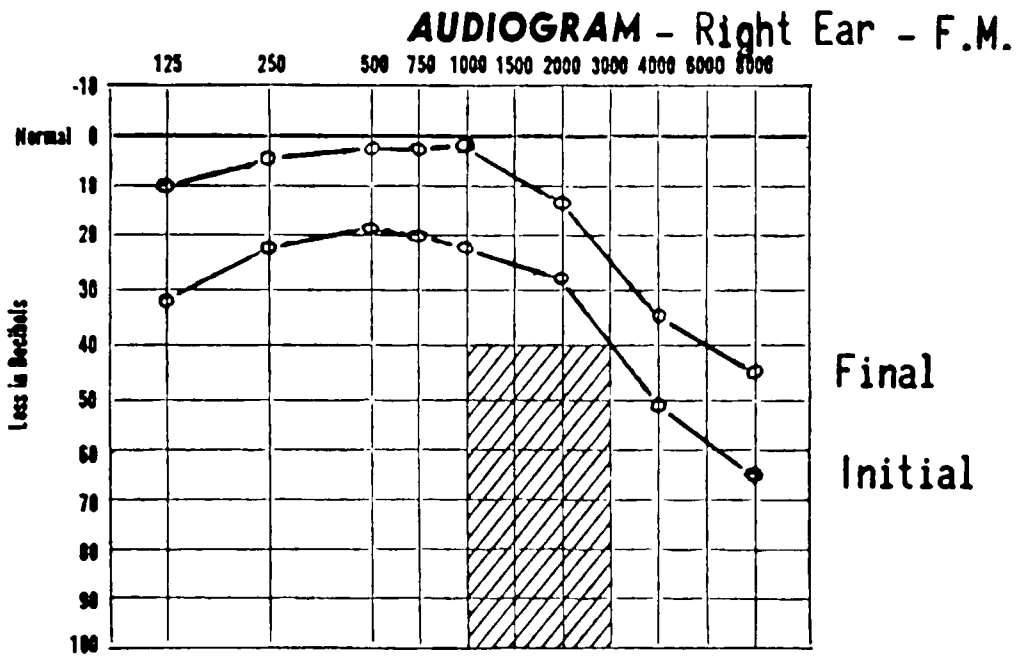


FIG. 147. Only a relative improvement is obtained in a case with alkaline pattern of impaired hearing.

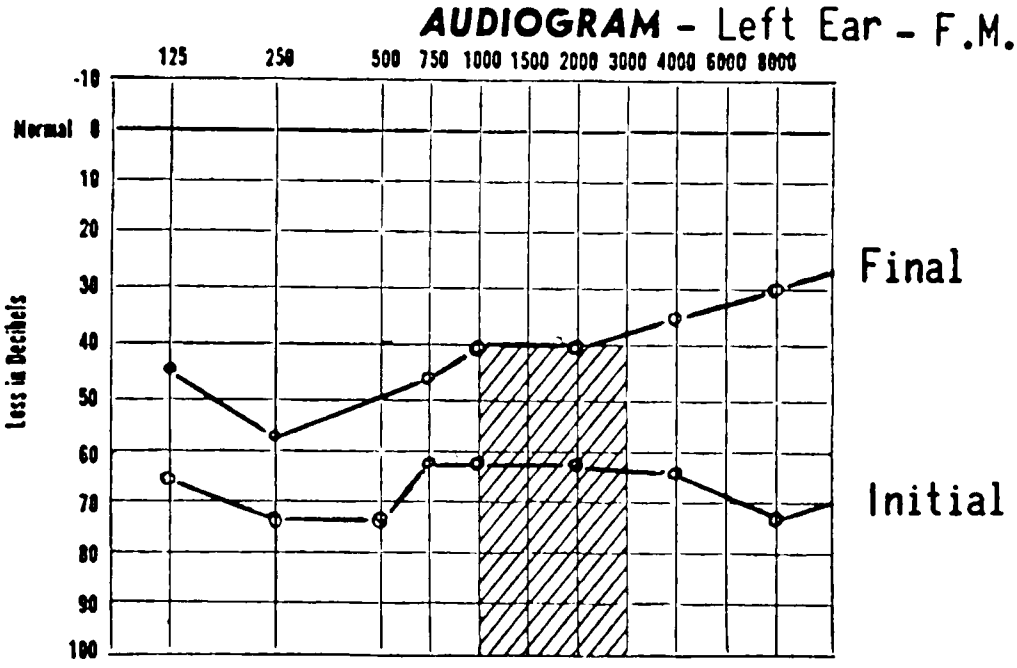


FIG. 148. A still smaller result is obtained in this case for the left ear.

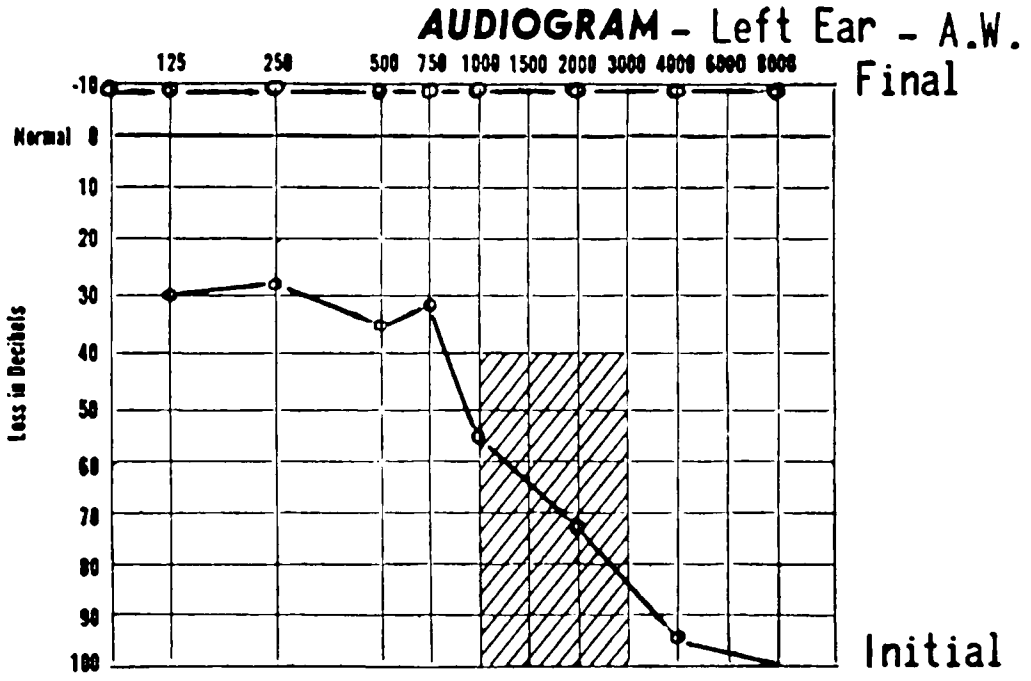


FIG. 149. An exceptionally good result is obtained for the left ear in the case A.W., in spite of an initially very impaired hearing.

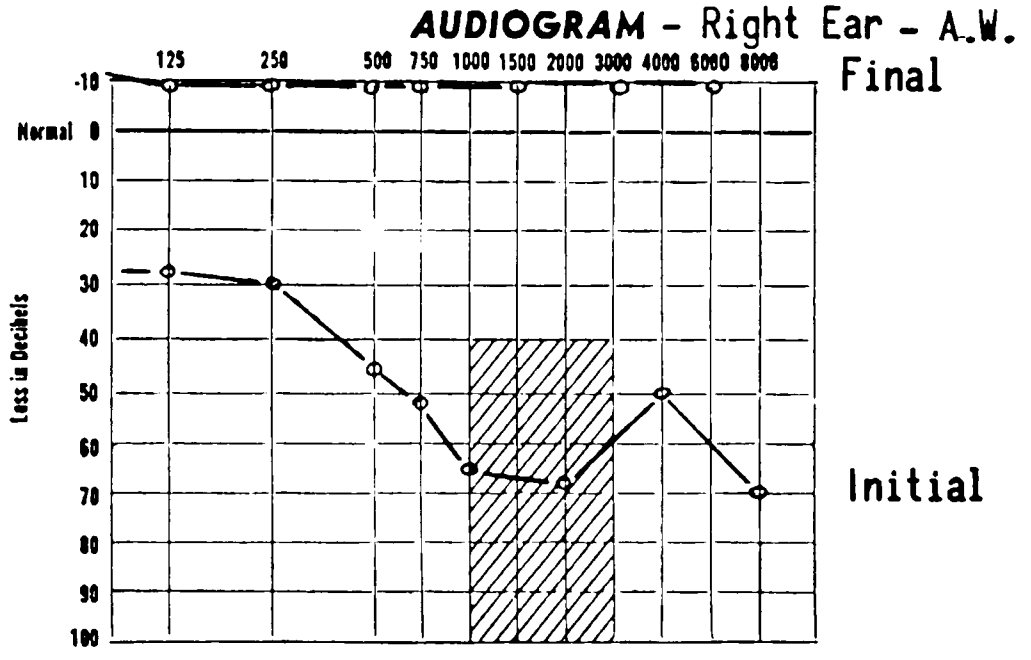


FIG. 150. Manifest improvements are obtained in this case with alkaline pattern of impaired hearing.

surgical cases can benefit from biochemical treatment which could prevent further sclerosis which often follows surgery. Application of this method in time to prevent deafness would be even more important than restoring hearing in far advanced cases.

Itching

Acid and alkaline patterns of itching have been recognized, and treatment based upon dual pathogenesis has been applied. The agent to be used is determined by the pattern found through analyses. Dosage, as for pain, is established according to the subjective response. Following these methods, many cases of intractable itching have been completely controlled. Of the group of agents with positive character, butanol and heptanol have produced the best results; in the opposite group, epichlorohydrin and sodium thiosulfate have been most effective.

Gallbladder and Renal Colic

Attempts were made to influence renal and gallbladder colic by using the same method. Butanol has shown little effect upon renal colic at least in the doses we tried. But the results in gallbladder colic were impressive. A 6.5% solution of butanol in saline injected intramuscularly, or even 15-30 cc. (one or two tablespoonsful) of 6.5% solution of butanol in water administered orally when the patient was not vomiting, controlled gallbladder colic rapidly. Only twice in more than 20 cases in which butanol was used was it necessary to give larger doses, such as 50 cc. of the same solution, to obtain the desired effect.

Arthritis

The analysis of the pattern of pain has shown that often in rheumatoid arthritis the pattern is alkaline, while in osteoarthritis, it is acid. Comparison of variations in pain intensity with changes in urinary surface tension helps to determine the pattern. However, with urinary surface tension values used as a guide both for agent and dosage, favorable clinical results have been obtained in cases resistant to other therapy. Arthritis, painful for many months, was controlled in many instances with several doses of heptanol or of sodium thiosulfate with epichlorohydrin and more recently with propionic aldehyde or sulfurized tetralin. The simplicity of treatment, total lack of undesirable side effects, and the long period of improvement

after even brief treatment in some cases, indicates that this method is worthy of further investigation. Some illustrations of the results are contained in the following observations:

Case #1

Mr. M. R., 63 years old with a long history of arthritic pains. Four years ago he was obliged to stay in bed for three months for severe pains in the right sacroiliac region. Two years ago he was again bedridden for a month and a half because of the same type of pain. A year ago, pain started again in the same sacroiliac region, to be followed by a very severe sciatica which kept him in bed for two months. Repeated X-ray examinations showed advanced arthritic lesions in the lumbar spine and around the sacroiliac articulation. About ten months ago, he suffered another similar attack, with severe pain, in the same region. Urine analysis made at this time showed an offbalance of the type D with low surface tension, low pH and high specific gravity. The blood serum potassium was high (5.3 mEq.). The patient was treated with agents of the group D—1 mg. of heptanol and 30 mg. butanol three times a day. The patient remained free of symptoms for four months, when similar severe pains were again present. This time analysis showed an offbalance of type A, with high urinary surface tension, high pH, low specific gravity and low blood serum potassium (4.0 mEq.). For this reason, different medication of the group A—5 mg. epichlorohydrin and 50 mg. sodium thiosulfate—were administered. The response was as rapid as previously and pain disappeared within a few hours. Since then the patient has been taking 5 mg. epichlorohydrin and 50 mg. sodium thiosulfate twice a day whenever the slightest pain appears. The clinical results are excellent, the patient being now able to move about entirely free of pain, as he has not been able to do for many years.

Case #2

Mrs. F. R., 60 years old, was bedridden for one and a half years about six years ago, with lumbar and sacroiliac arthritic pains. X-ray treatments, short wave, ionization with histamine and ultrasonic treatments appeared entirely ineffective. The administration of urolytic agents had helped at this time. The pains recurred repeatedly in the last three years keeping the patient in bed for from one week to three months at a time. For the past eight months, the patient has been under treatment using medication of the group A or D, according to the urine analysis. With this treatment the pain has been completely and rapidly controlled, never lasting more than a few hours.

Case #3

Mr. N. K., 55 years old, suffered for many years with generalized and very painful rheumatoid arthritis. Prior to coming under our care, he had been bedridden for six months, entirely immobilized with severe pain in arms, back and legs. The patient was entirely incapacitated, unable even to feed himself. Treatments with different cortisone preparations, ACTH, gold, etc., provided practically no relief of the severe pains. He came under our care, entirely immobilized and in severe pain. According to the analysis which showed a low urinary specific gravity, and pH, high surface tension and a low blood serum potassium, the patient received medications of the group A, sodium thiosulfate, epichlorohydrin and heptyldiselenide. Under this medication the patient made a most dramatic recovery. Within a few days, the patient was out of bed without pain, walking normally and with full functional capacity of his arms and legs. While still under treatment the patient went back to entirely normal activity. He gained 35 lbs. in the last months.

Connective Tissue Conditions

We have discussed previously the hypothesis that corticoids actively intervene in the synthesis of an entire group of substances in the organism. The energetic formation between C_{11} and C_{21} of these corticoids would act as a mold or template to attract and keep various radicals in special reciprocal position, thus favoring, as a second step, the synthesis of new substances. These substances would vary according to the energetic formation of the corticoid. In one group, which could be called the "gluco" group, we identified glucose, glucuronic acid, glucosamine, galactosamine, glucosaminic acid, galactosaminic acid, and some other uronic acids. Even ascorbic acid could be related to such a synthesis mechanism.

We investigated some of these substances, particularly in relation to the therapeutic properties of corticoids. In 1951, we chose glucosamine as a substance closely corresponding to the template of cortisone. Glucosamine treatment was used in patients with pemphigus, rheumatoid arthritis, psoriasis, ocular condition and allergy. The following cases illustrate the results obtained.

Mr. H. S., 46 years old, had generalized psoriasis. In the last twelve years, the lesions had progressed continuously to cover more than 75% of his skin. Local treatment had had little effect. Cortisone injections cleared the skin in two weeks but not completely. With

cessation of treatment, the condition returned. The patient remained without treatment for a few months before beginning our treatment: 5 cc. injections of glucosamine 10% solution administered daily. Changes were seen in 3 days, with the lesions becoming paler and less scabby. With two injections daily, the skin was almost entirely normal in about 10 days, only a few lesions remaining. Continuation of the treatment for another week did not make these disappear. Upon cessation of treatment, the lesions regressed to their previous dimensions. In a second course of treatment, with two daily injections of 5 cc. of a 10% solution of glucosamine in saline, the lesions cleared but reappeared when treatment was discontinued.

We also treated a series of cases of rheumatoid arthritis and found that subjects, who had previously responded well to cortisone, also responded to glucosamine.

Mrs. B. B. had rheumatoid arthritis of the left knee and both hands. Pain and swelling were severe. The patient had responded fairly well to cortisone, but due to retention of water, this treatment was discontinued. In less than 10 days, the arthritis returned. The patient was given glucosamine injections. At first, 5 cc. of the 10% solution in saline was injected once a day. Later, 3 injections daily were used. The symptoms, which had decreased with the lower doses, were fully controlled by the 3 daily injections. Pain and swelling fully disappeared. Moon face was not observed. The treatment was continued with 2 injections daily and, after one week, one injection daily. With this dose, pain and swelling returned. Resumption of 3 injections a day controlled them again. The treatment was discontinued because of the apprehension of the patient over receiving 3 injections daily of 5 cc. each. A mixed treatment with a lower dose of cortisone and one injection of glucosamine daily was continued with satisfactory results for a few weeks, after which the patient stopped her visits.

We treated cases of rheumatoid arthritis with oral glucosamine with fair to good results. Four grams of glucosamine a day appeared to be the minimum requirement. Good results could be seen in some cases after doses of 5 to 10 grams daily. These results were confirmed by B. Welt who, following his research, used the same preparation of glucosamine on a series of 15 patients bedridden with arthritis at the Greenpoint Hospital in Brooklyn, New York. Subjective and objective improvement occurred in patients with rheumatoid arthritis while no changes were seen for those with osteoarthritis.

For more than one year, Welt has treated a case of pemphigus with injections of glucosamine and has been able to prevent the appearance of new lesions.

In a few cases of iridocyclitis, treatment with glucosamine (2 injections of 5 cc. of the 10% solution daily) healed the lesions in two or three days.

Galactosamine produced results almost similar to those of glucosamine. Still better results were seen with glucosaminic acid, used in the same doses as glucosamine. Some strikingly good results in several cases of arthritis were obtained with gluconic acid administered orally in doses of a few grams a day (four tablespoons of a 25% solution).

Hemorrhage

In studying hemorrhage, it seemed necessary first to define precisely the conditions under which this important episode occurs, as we did for pain, itching, etc., since the course of hemorrhage, and particularly its response to treatment, seems to depend greatly upon certain peculiarities related to its pathogenesis. Hemorrhage results from a break in the continuity of a blood vessel, which can be induced by an external influence on a previously normal vessel, or can occur as a result of processes taking place in abnormal vessels. We have called the first type of hemorrhage "accidental" or "traumatic" and reserved the term "pathological" for the second, which appears to be a direct result of pathological changes in a vessel. The latter term is used in the same sense as it is used for fractures where "pathological" indicates only preexisting lesions in the bones.

In a traumatic hemorrhage, the therapeutic problem is limited to stopping the flow of blood. Mechanical means to close the bleeding vascular wound or agents able to increase the capacity of the blood to form clots can be used. They represent the only approach in accidental hemorrhage.

In pathological hemorrhage, other problems arise. The knowledge of the local pathological changes, which lead to the appearance of bleeding, is important both for preventing and controlling hemorrhage. The pathogenic factor involved will be considered along with the problem of hemostasis.

Hemorrhagiparous Agents

Local and general factors are involved in pathological hemorrhage. Ulcerated lesions provide a favorable condition. So does local infection. Anticoagulants may act indirectly upon blood vessels.

Hemorrhagiparous properties of some substances became evident during research on their therapeutic use in cancer patients. For example:

P. T., a patient with carcinoma of the floor of the mouth widely ulcerated in the submaxillar region, bled sporadically from the lesion.

When a dose of 20 drops of Coramine (brand of nikethamide) was given for his general condition, a relatively severe hemorrhage appeared immediately afterward. There was another hemorrhage when a similar dose was administered 12 hours later. Suspecting a correlation between hemorrhage and medication, medication was discontinued and there was no hemorrhage during the following two weeks. When only 10 drops of Coramine solution was given again, a new hemorrhage appeared. After two more weeks without Coramine and without hemorrhage, a new dose was given to check the correlation between medication and bleeding, and was followed again by hemorrhage.

Reviewing cases lost through hemorrhage, we could find several in which lethal bleeding was preceded by administration of Coramine in the usual dose. This hemorrhagiparous effect was noted so consistently as to make us discontinue use of Coramine in cases with ulcerated lesions.

Alerted by this experience, we noted hemorrhagiparous activity in other agents. Glycerol, we found, could induce severe bleeding even when administered in doses as low as 5-10 drops, and two lethal hemorrhages were traced to such doses. Thiamine chloride in therapeutic doses—such as 100 mg. injections—produced hemorrhages. A similar hemorrhagiparous effect was noted for isamine blue. Glucose, administered intravenously in large doses to patients with ulcerated and infected cancerous lesions who had previously hemorrhaged, induced new bleeding. We must emphasize that all the hemorrhagiparous agents produced the bleeding effect, especially in subjects who had previously had hemorrhages from their lesions. This would indicate the importance of local changes. In such patients, other agents also induced bleeding. In some cases of gastro-intestinal cancer, bleeding followed a normal dose of aspirin. But even in lesions which had never bled, the first group of hemorrhagiparous agents—Coramine, glycerol and thiamine—could induce bleeding.

In trying to correlate the pathogenesis of these hemorrhagiparous effects with existing offbalances, an interesting relationship was noted. A tendency to bleed was found to be promoted by sterols. Administration of cholesterol in doses as high as 5 cc. of a 2% solution in oil, two or three times a day, for several days, was followed by hemorrhage in patients with ulcerated lesions. This occurred only in a few cases. But a high sensitivity to other hemorrhagiparous agents often developed. The administration of minimal doses of glycerol produced bleeding in subjects treated with cholesterol and did so even more frequently when large amounts of insaponifiable fraction of organs were administered.

Hemorrhages which follow administration of these hemorrhagiparous agents are usually severe and of arterial character. Examination of such bleeding lesions has revealed transverse severance of small or even medium arteries. Only rarely was there oozing bleeding from capillaries or small veins. In several cases, administration of hemorrhagiparous substances induced petechiae or purpura, but this occurred only when thrombopenia was also present. The petechiae were seen at sites where local circulatory impairment already was present. We believe that this hemorrhagiparous effect must be emphasized for its clinical importance. Products such as Coramine (nikethamide) and thiamine are widely used as therapeutic agents and glycerol is a common vehicle for pharmaceutical preparations. Therefore, we must bear in mind their possible role in hemorrhages. In subjects with ulcerated lesions, their administration has to be banned or special precautions must be used. The same precautions have to be taken for the use of glucose in cases in which a previous hemorrhage has not been controlled by mechanical means.

Antihemorrhagic Agents

Butanol

In 1943, during research studies concerning the pharmacological activity of glycerol on abnormal foci, its hemorrhagiparous effect appeared as a serious handicap. Various hemostyptic substances were tested without sufficient effect. At this time, a new product, to which a hemostatic effect was attributed, appeared on the market. It was a very weak solution (around 1/10,000) of octanol in saline. We could find no therapeutic effect for it. However, we were studying butanol and other higher aliphatic alcohols with lipoidic properties, and we decided to test butanol for its antihemorrhagic activity, hoping that it might counteract the undesirable hemorrhagiparous effect of glycerol. It did and we have since added butanol to glycerol for this purpose.

We observed the remarkable hemostatic effect of butanol years later in a patient with severe hemorrhage, to whom doses of 10 cc. of a 6.5% solution were given intravenously. Hemorrhage stopped in a few minutes. Since then, we have successfully applied butanol clinically in hemorrhages of various origins.

As an antihemorrhagic agent, butanol is administered either parenterally as a 6.5% solution in saline, or orally as 6.5% solution in water. The route of administration—intravenous, intramuscular, subcutaneous or oral

—is chosen according to the severity of the hemorrhage. Doses of 5-20 cc. are given and repeated, if necessary, at intervals of a few minutes. Since butanol is not at all toxic in these large doses, we usually give them with good results in severe emergencies. The following cases illustrate the styptic effect.

R. E., a 64-year-old man with an extensive ulcerated epidermoid carcinoma of the floor of the mouth and large bilateral cervical metastases, had received intensive radiotherapy. Occasionally, there was a small amount of bleeding from the oral lesion, but a sudden hemorrhage of about 500 cc. of blood during a half hour period occurred late at night while the patient was at home. Pressure, applied to the floor of the mouth, was of value but bleeding recurred immediately upon release. Oxidized gauze, adrenalin soaked gauze, vitamin K and vitamin C in large quantities were of no value. n-Butanol solution in saline was finally obtained and 5 cc. injected intravenously. Bleeding ceased during the injection. A second equally severe hemorrhage occurred one week later and again could not be adequately controlled by pressure or oxidized gauze. 10 cc. of n-butanol solution administered intramuscularly stopped the bleeding within 2-3 minutes. Three hours later, the floor of the mouth was carefully examined preliminary to right external carotid artery ligation, and the lesion was found to be free of bleeding. Despite the ligation, bleeding later recurred but was controlled each time by n-butanol administered orally.

S. S., a 30-year-old man, had an adenocarcinoma involving the right maxillary sinus with cervical metastases. During the period of observation, this patient experienced a profuse hemorrhage from nose and mouth. Blood flowed at the rate of approximately 5-6 cc. per minute, and pressure gave little or no relief. 5 cc. of n-butanol in saline solution was injected intravenously and within two minutes, the profuse hemorrhage ceased and did not recur at that time. On several other occasions, bleeding was controlled following the administration of oral doses of 5-10 cc. of 6.5% n-butanol solution in water.

A. M., a 36-year-old man, had multiple pulmonary metastases from a primary malignant melanoma of the left foot. On several occasions, hemoptysis occurred and during three of these episodes bleeding was profuse. 5 cc. of n-butanol in saline administered intramuscularly stopped two of these episodes rapidly, but in the third, an injection of 10 cc. intravenously was needed ten minutes after an initial intramuscular dose. Although the intramuscular injection was ineffective, the bleeding was halted within two minutes after intravenous administration.

In a report in 1951 in "Angiology," (193) we presented the following statistics concerning the control of hemorrhage in cancer cases:

	Group I Untreated	Group II n-Butanol
Number of cases observed	256	344
Number of cases with profuse hemorrhage	18	25
Percent of cases with profuse hemorrhage	7	7
Number of deaths attributed to hemorrhage	12	1
Percent of deaths in cases with profuse hemorrhage *	67	4

* Death attributed directly to hemorrhage.

Since then, these results have been consistently confirmed.

Additional progress was achieved with organic acids added to butanol in adequate amounts. Completely non-toxic in the dosages used, they were observed to enhance the hemostatic effect of butanol. This hemostatic effect has been confirmed many times, particularly in Europe where, following our research, butanol has been widely used as a hemostyptic agent.

A hemostatic effect was also evident when butanol was used with the principal aim of controlling pain in postoperative cases. The hemostatic effect was especially important in cases where pathological bleeding usually represented a major complication, either because of the impossibility of obtaining hemostasis during operation or because the surgical wound could not be kept aseptic, as in tonsillectomy, prostatectomy and plastic surgery of the nose. In a study on the use of butanol for postoperative care in tonsillectomies, B. Welt has been able to show a preventive effect, and more important, a hemostatic one if hemorrhage occurs. (187) *(Fig. 91)* In prostatic surgery, the amount of bleeding was so reduced, that of a group of 40 cases, only one needed transfusion while in a similar number of controls, 8 had to have transfusions. (189)

Still more impressive results have been noted in pathological hemorrhages following plastic surgery, especially of the nose. In a significantly large number of cases, severe hemorrhages tend to occur around the 7th day after operation. We have discussed above the pathogenesis of these hemorrhages and the relationship to the allergic defense mechanism. Such hemorrhages have been difficult to control. The use of antibiotics has only partially reduced their frequency and gravity. S. Scher has obtained very good results with the administration of butanol in such cases, using an injection of 5 cc. of a 6.5% solution of butanol once before surgical intervention and four times daily for two days afterward, followed by oral administration of 15 cc. or one tablespoon four times a day for eight days. No hemorrhages occurred in more than two thousand cases treated. In a

few patients who neglected to take the medication, and in whom a hemorrhage appeared, bleeding was rapidly controlled by butanol. *(Note 6)*

Experimental Research on the Hemostyptic Effect: In a series of studies we sought to find the mechanism by which butanol controls hemorrhage. In an investigation carried out in our laboratory, M. Bier and P. Teitelbaum (194) showed that individual members of the homologous series of aliphatic alcohols decrease the degree of retraction of clots when added in vitro to blood. *(Figs. 141 to 143)* By varying the amounts added, this effect was observed to occur only at values above a critical concentration of the alcohol in blood. Bier could show that the critical value, which differs for members of the homologous series, is proportional to the lethal toxic dose in mice.

This non-retraction of clots in vitro also can be recognized in cases treated with butanol through the gelatinous aspect of the clots at the moment when the hemorrhage stops. However, it is interesting to note that the amount of butanol injected, considered in terms of the amount of the circulating blood, results in concentrations considerably below the critical values needed to produce this effect in vitro. However, concentration of butanol at the site of the wound may explain this. It is also of interest that the same gelatinous character typifies the clots which remain attached to bleeding lesions in animals treated with butanol. In mice, when a portion of tail was cut and butanol was used, the abnormally long clot remained adherent to the wound, differing from that seen in controls.

In spite of changes in the clot, it seems that the effect upon the blood itself, and its coagulation in a wound, represents only one of the means through which butanol controls hemorrhage. The speed with which butanol acts, often within seconds after intravenous injection, is much greater than blood coagulation time. Consequently, changes in clot formation alone do not appear sufficient to explain the mechanism through which the rapid hemostasis occurs.

M. Bier and H. Lerner in our laboratory studied the influence exerted by butanol upon hemorrhage induced by the highly active proteolytic enzyme, ficine. (195) They were able to induce standardized hemorrhages by injecting ficine solutions under the skin of the abdomen of white mice. *(Fig. 151a)* (In other animals and with other sites of injection in mice, the individual variations were too great to make the resulting bleeding useful as material for testing the effect of agents upon hemorrhage.) With adequate doses of ficine, severe hemorrhages followed by skin ulcerations were induced. The bleeding, and even the ulcerations, were almost entirely prevented when butanol was administered. Figure 151b shows the results of

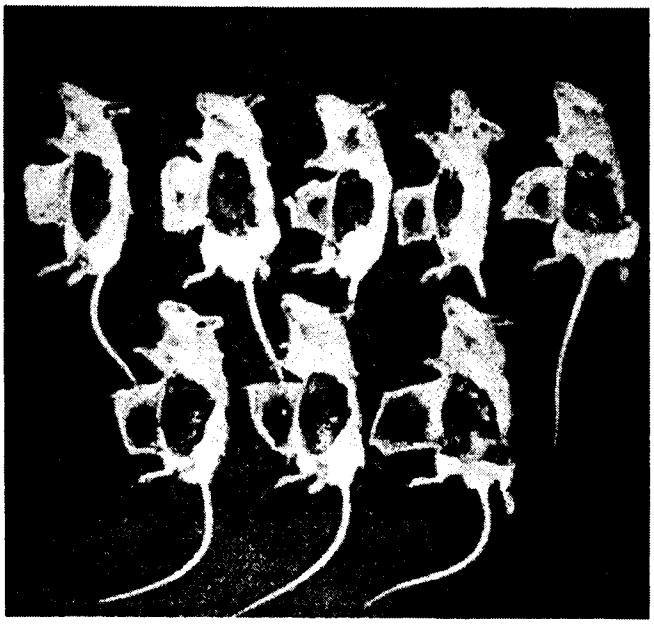


FIG. 151a. Shows graded extent of hemorrhagic infiltration obtainable with progressive amounts of ficin injected subcutaneously in the abdominal region in mice.

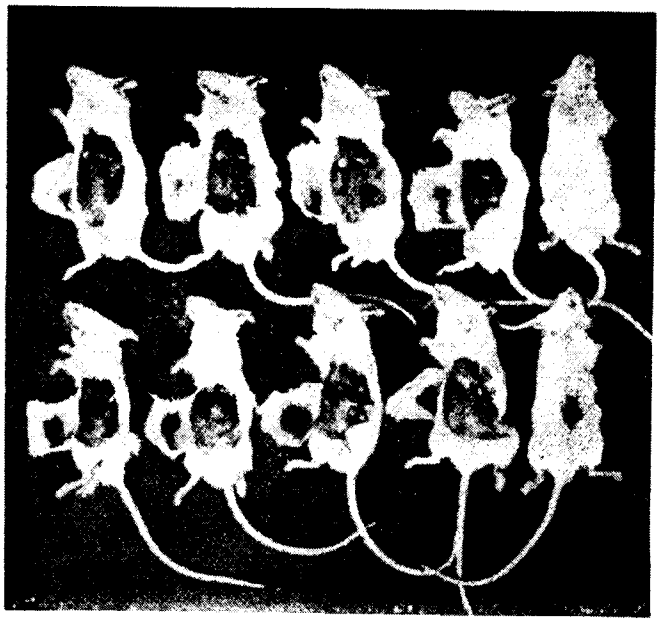


FIG. 151b. The influence exerted by butanol upon the hemorrhage induced by ficin injection.

Top Row. Comparative group treated with butanol. Last animal in each row shows the external appearance of the site of the injection while in others, the skin flap was separated.

Bottom Row: Ficin injected animals.

this experiment, with the manifest differences, following ficine injections, between animals receiving butanol intraperitoneally and controls.

The antifibrinolytic activity of butanol (196) could explain its intervention in protracted bleeding, and especially in cases where the effect of butanol appears after hours or days. However, inhibition of fibrinolytic activity cannot be conceived to intervene in an action taking place in less than a few minutes.

In trying to explain butanol's antihemorrhagic effects, we also considered its pharmacological activities. We have noted the action of butanol upon the acid-base balance of abnormal tissues, as shown by changes in the pH of the second day wound crust. In abnormal tissues, butanol reduces local pH but it does not do this to any great extent in normal tissues. This led us to investigate the difference in the influence of butanol upon pathological hemorrhages. The immediate bleeding induced by standard cutting of the tail in mice was not constant and, in general, was not markedly influenced by administration of butanol. But there was a marked effect upon hemorrhage induced by the displacement of the clots through mechanical maneuvers one to two hours after cutting of the tail. In controls, the bleeding lasted almost the same length of time as bleeding from fresh lesions, while in animals treated with butanol, it often stopped in a very short time.

These data, although interesting, did not seem to offer a completely satisfactory explanation of the mechanism by which butanol stops bleeding, especially in cases in which it acts within minutes or less. It appeared improbable that the formation of a clot alone would stop the hemorrhage under these conditions. An interesting observation led us to another hypothesis.

In several patients with wide ulcerations, we were able to examine the hemorrhaging vessel after bleeding had been stopped by butanol. Contrary to all expectations, we found that the artery, which usually was severed transversely, was not buried in a clot but remained almost isolated and somehow separated from it. It seemed that blood vessels themselves might have a role in hemostasis. The intervention of a spasm of the smooth muscles of the vessels was considered. This was indirectly confirmed when a patient with severe and prolonged bleeding from the bed of a prostate after ablation, was treated with butanol. An intravenous injection of 40 cc. of butanol was followed by such violent contraction of the bladder as to expel, with great force, the catheter together with clots and urine present in the bladder. At the same moment, bleeding, which had persisted for more than a week, stopped suddenly. We connected this sudden spasmodic contraction of the smooth muscles in the abnormal bladder with

the injection of butanol and considered that butanol might produce a spasm of the muscular walls of abnormal blood vessels—abnormal because of the hemorrhagiparous condition itself. This would explain the rapidity of the hemostatic effect and the selective action upon small and medium arteries with important muscular walls. In fact, we saw that, while very severe arterial hemorrhages were completely stopped in less than one minute after an intravenous injection of butanol, the same effect was not obtained in oozing bleeding.

We tried to investigate further this spastic effect upon blood vessels as the mechanism in butanol hemostasis. Experiments with isolated aorta preparations of rabbits and rats showed that a spastic effect cannot be induced by butanol, even if the vessels previously have been harmed by manipulation. This can be explained by the fact that the aorta does not have muscular fibers. The same lack of spastic effect is seen in normal arteries of the hind legs of rats and frogs.

The administration of butanol to an animal after a small branch of the mesenteric artery was first crushed and, after some time, cut, produced a spastic effect which transformed the jet-like hemorrhage into an oozing one, greatly reducing the blood loss. The hypothesis of vascular spastic contraction as the mechanism in butanol hemostasis has received further indirect confirmation through the study of the effect of butanol upon hemorrhage induced by single traumatic lesions in various organs. Differences were observed according to organs or tissues affected. While bleeding liver wounds are influenced only to a small degree by intravenous administration of butanol, hemorrhage from a kidney wound stopped rapidly. The fundamental difference between the liver portal circulation with minimum muscularity of the vessels, and that of the kidney, where highly developed artery muscular layers are seen, can explain the unequal response to butanol.

As we can see in these cases, the contraction of a pathological artery can insure rapid hemostasis and accords with the fact that the artery is not buried in a clot. This explains why, especially in clinical application, butanol is more active upon arterial hemorrhage and much less active upon capillary bleeding. This mechanism also would explain the same good effect upon hemorrhage from veins with important walls. Failure of butanol seen in three cases of hemorrhage from varices of the inferior esophageal veins can be explained by the almost complete lack of muscular layers in these varicose veins, which would bar a vasculo-muscular contraction.

Parallel to these studies, other possible hemostatic mechanisms have been investigated. We tried to interpret the unusual fact that butanol

stopped hemorrhage while agents such as nikethamide, thiamine, isamine blue, sterols and glycerol induced bleeding—yet all have positive polar groups in their molecules, represented by an amine or amide radical for most of them and by hydroxyls for glycerol and sterols. As we have mentioned before, all agents with such positive radicals induce a shift toward less alkaline values for the second-day-wound-crust pH. Therefore, this could not be considered to be the factor that determines the antagonistic effects on bleeding. The aliphatic or cyclic character of the nonpolar group does not seem to be a factor since glycerol and butanol both have aliphatic chains.

However, correlation with another biological effect could be noted. All the substances with hemorrhagiparous effect, also produce a convulsive effect if administered in sufficiently high doses. The convulsive effect of Coramine and thiamine has been known for a long time and we used these substances any time we wanted to induce experimental convulsions. We also have seen that convulsions can be consistently induced in animals through the use of relatively large doses of glycerol or sterols. Convulsions in several human cases have followed the use of these agents. Doses as high as 20 cc. of a 5% solution of the insaponifiable fraction of placenta or of the 2% solution of cholesterol in oil, administered for therapeutic purposes have induced convulsions in patients, with a previous history of convulsive seizures. A convulsive effect in animals has been noted for all the agents mentioned above which also have hemorrhagiparous activity. We were able to induce convulsions in rats, even by injecting 20 cc. of a solution of 10% glucose subcutaneously once a day for a few days. In humans, we also saw convulsions appearing after glucose was administered intravenously in an amount of 100 gm. in a saline preparation to patients treated concomitantly with desoxycorticosterol, although the last substance has no convulsivant effect by itself.

On the other hand, the antihemorrhagic butanol produces a hypnotic effect if administered in high doses. The dose of butanol needed to prevent hemorrhage induced by ficine in mice, for example, was enough to provoke hypnotic activity comparable to that of barbiturates, chloroform and even ether. Very interesting is the fact that these agents also are able to prevent ficine-induced hemorrhage if administered in doses sufficiently high to produce hypnotic or narcotic effects. The peculiar correlation between convulsive and hemorrhagiparous effect on the one hand, and hypnotic and hemostatic effect on the other, provides some further understanding of butanol hemostasis, but does not furnish the explanation for the mechanism through which this hemostasis takes place. The most plausi-

ble conclusion is that butanol intervenes through several mechanisms, some inducing immediate hemostasis through arterial contraction, while others have a later effect through changes in the blood clotting process, with lack of retraction of the clot and an influence upon fibrinolysis.

Contraction would explain why, with only few exceptions, it is the pathological arterial hemorrhage which responds most favorably to butanol. An immediate influence upon capillary or venous hemorrhage is less manifest and, in a very few cases, absent. The same is true for traumatic hemorrhages where, although there are some good immediate results, in general they are less rapid than for pathological arterial hemorrhage. Because of its immediate effect upon arterial bleeding, butanol became the agent of choice for those pathological hemorrhages which, through their arterial origin, could be fatal in a short time.

One of the big advantages of hemostasis induced by butanol over that obtained through other agents resides in the fact that there is no manifest increase in blood coagulability. Only in concentrations which never can be attained in vivo has butanol been seen to change the coagulability of blood. The inherent danger of thrombosis resulting from high blood coagulability limits the amount of the other agents to be administered. This danger does not exist for butanol and no such limitations are placed upon its use. The fact that normal prothrombin time is uninfluenced by butanol while high prothrombin time is reduced toward normal represents another advantage.

In further studies, we tried to enhance the hemostatic action of butanol without increasing blood coagulability. The addition of calcium salts was of no value but an enhancement was seen with potassium salts.

In a series of experiments, it was noted that, when a solution of butanol is kept for a long time in a stoppered bottle, its activity increases. For long-standing preparations, 50% smaller doses were sufficient to protect mice against the action of ficine. The narcotic and toxic effects of these preparations also increased in the same proportion. This led us to add butyric aldehyde, the product of immediate oxidation of butanol, which increased butanol's coagulating effects only very slightly but enhanced its hemostatic effect considerably. The addition of hydrogen peroxide did much the same.

Blood Mixed with Butanol, used against Hemorrhages

S. Akad, working in our laboratory, showed that the coagulation time of blood is also increased if butanol, mixed previously with blood, is added. In the clinical application of this observation, we used the patient's own blood extemporaneously mixed with butanol. In a syringe containing, for

instance, 10 cc. of the butanol solution, 2-5 cc. of the patient's blood is withdrawn. After mixing them, and without removing the needle from the vein, the contents of the syringe are injected intravenously. A similar mixture can be injected also intramuscularly or subcutaneously. The results have been very good. In some cases in which butanol alone was not able to stop a hemorrhage, the blood-butanol mixture did. With this special technique, we have been able, in recent times, to bring most hemorrhages under control within a few minutes.

The fact that agents with positive polar groups, such as sterols, glycerol, coramine, thiamine and others, have hemorrhagiparous activity led us to try to influence hemorrhage with agents considered biologically antagonistic through their negative polar group.

Many years ago, experimenting with chlorine solutions in saline, we observed a manifest effect upon coagulation time. Intravenous injection of such solutions brought coagulation time to values as low as one minute. The addition of these solutions to butanol greatly increase its effect in vitro upon coagulation time but had less effect upon hemostasis in vivo. Similar but somewhat less manifest effects were obtained by adding hydrochloric acid to butanol solution. On the other hand, organic acids such as oxalic, malonic, citric, lactic maleic or citraconic showed a favorable effect. Without changing coagulability of the blood, these acids were seen to increase the hemostatic effect.

Fatty Acids

The same antagonism to sterols and glycerol led us to use fatty acids from cod liver oil. (197) While results in severe large arterial hemorrhages were not impressive, the effect upon oozing capillary, venous and small arterial hemorrhages was very good in a large proportion of cases. For example:

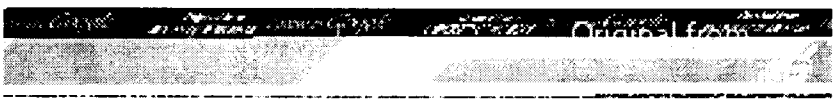
> N. V., 57 years old, with multiple pulmonary metastatic lesions from a hypernephroma, had frequent hemoptysis. At times, the bleeding became more accentuated, the patient expectorating clots as well as uncoagulated fresh blood. Intramuscular administration of two doses of 10 cc. of a 6.5% solution of butanol at half hour intervals had little influence upon the bleeding. Intramuscular administration of 1 cc. of a solution of 10% of the mixture of fatty acids obtained from cod liver oil stopped the bleeding in less than 20 minutes, with the effect persisting for more than two months. A new episode of oozing bleeding was again immediately controlled by injection of the fatty acid preparation.

Other cases with hemoptoic sputum, prolonged bleeding from gastric or duodenal ulcers or from rectal or uterine tumors, all corresponding to oozing rather than to acute massive hemorrhage, have responded to administration of this fatty acid preparation. Almost uniformly, these oozing hemorrhages, which had not responded to butanol, were rapidly controlled. We now use butanol mixed with small amounts of hydrogen peroxide and organic acids mentioned above, to control severe arterial hemorrhages while for the oozing type, fatty acids from cod liver oil are used.

Allergic Conditions

Allergic conditions, which as seen above, are related to the defense mechanism, also have been integrated into the general therapeutic approach. This has largely permitted us to apply to such conditions the same therapeutic measures used in general. The study of the manifestations has, however, shown that except for the anaphylactic shock, the clinical allergy corresponds to the prolonged phase with the predominance either of sterols or lipoacids. The urinary surface tension has appeared as a valuable criterion to indicate the occurring offbalance. In cases with a high urinary surface tension, sodium thiosulfate, aldehydes or epichlorohydrin have given particularly good results, while the cases with low surface tension showed favorable response to heptanol and butanol. Food allergies, asthma, urticaria which had persisted for years and were insufficiently influenced even by corticoids—have responded with the complete disappearance of their manifestations with an adequate dose of one or the other of the medications mentioned above. In most of the cases kept under continuous treatment with minimal doses, favorable results persisted even after the subjects were again under the influence of antigens. The following observations illustrate these results.

Mrs. M. S., 45 years old, with skin and eye allergic manifestations, highly sensitive for the past six years to fish, eggs, alcoholic beverages, some vegetables and fruits, and especially to dogs, showed no favorable response to corticoids. With high urinary surface tension and high eosinophiles, the patient was treated with 50 mg. sodium thiosulfate and 2 mg. epichlorohydrin, four times a day. The symptoms decreased progressively to disappear in a week. After a month's treatment, she was able to take—without any inconvenience—foods and alcohol to which she had been previously sensitive. After another two months, the acquisition of three puppies produced no disagreeable effects. The patient has continued



on the same treatment, but reduced to twice a day, for the past year without recurrence of the manifestations.

Mr. A. L., 58 years old, had frequent attacks of asthma for over four and a half years which left him unable to work for the past year. Because of low urinary surface tension, the patient was put on butanol—5 cc. of a 6.5% solution in water—to be taken every six hours. Although the first doses showed marked objective and subjective changes, the treatment was continued. The patient was free of attacks for four months at which time he stopped medication. Two weeks after stopping medication, he had an attack, the first in four and a half months and this was followed by another the following day. By resuming the medication, he has been free of symptoms for more than a year.

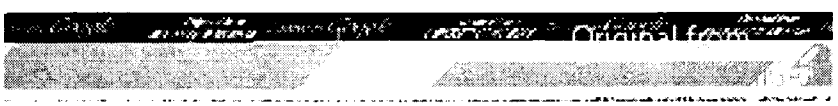
The possibility of preventing allergic manifestations with butanol, which appeared so clear in the traumatic lesions, opens an entirely new view for many conditions where such a pathogenesis intervenes.

The concept of a nervous tissue allergy intervening in the pathogenesis of multiple sclerosis, led us to try similar antiallergic treatments. The low surface tension led us to utilize as agents, lipoids with a positive character. Interesting—although not constant—results were obtained with insaponifiable fraction of cow brain. Good results were obtained with butanol—100 mgr. four times a day—together with an antihistamine preparation.

ARTERIOSCLEROSIS

One of the most important medical problems from all points of view—pathogenic, therapeutic and even social—since it still represents the chief direct cause of death in most civilized societies, is that of arteriosclerosis. The fact that lipids seem to intervene in its pathogenesis, has led us to consider this condition from the point of view of biological offbalances. With the development of our research, we tried to apply to this condition a systematic analysis in accordance with the basic concepts presented above. This attempt has permitted us to arrive at some new views which will be discussed briefly here.

The analysis of the specific manifestations of arteriosclerosis from the point of view of *organization,* that is, as related to the different levels, led us to recognize that it represents a condition principally limited to the level organism, and more especially to its secondary part, the circulatory system. Many of the fundamental characters of the condition could be explained by the relationship of this level to other levels of the organization, as we will see below.



From the point of view of the *dualistic concept*, it was easy to see that arteriosclerosis corresponds to an offbalance type A. All the analyses concerning the systemic level show patterns which indicate this offbalance. High urinary surface tension, low urinary specific gravity, high urinary pH, low urinary sulfhydryl index, found in the routine analyses point to such an offbalance. The long persistence of the skin wheal seen in the subjects analyzed, confirms this diagnosis. The fact that some manifestations of arteriosclerosis can be induced experimentally in animals through the administration of cholesterol, has placed into limelight the pathogenic role of cholesterol. While its administration in high amounts to rabbits or cockerels induces atheromas, it does not induce the complex condition itself. Usually the animals return to normal, even with a rapid healing of their atheromas after the suppression of the administration of cholesterol. Although hypercholesteremia represents thus only one pathogenic factor, it appeared interesting to investigate its intervention in the condition.

The relationship of cholesteremia to arteriosclerosis is certainly not a simple one. The total amount of cholesterol in blood alone, in its free form, and the macromolecules of certain dimensions resulting from their bond to the other constituents of the blood, although related to arteriosclerosis, do not seem to represent by themselves the pathogenic factor of this condition. This latter seems to be related to a more specific intervention of this substance at the level of the blood and circulatory system. Research in this field has led us to recognize this special intervention.

It is a known fact that the appearance of crystals of cholesterol in the cells of the intima of the arteries and in the cells of the vasa vasorum represents an essential factor in the pathogenesis of atheromas. Study of the capacity of blood serum to dissolve or, on the contrary, to precipitate cholesterol has permitted to link it with the appearance of specific arterial lesions in this condition.

In this study, we used the procedure originally devised by Policard when he investigated the relationship of cholesterol and arthritis. Blood is obtained through veinous puncture and the serum is separated aseptically. The amount of total cholesterol is determined in the blood serum. A sterile crystal of cholesterol is added to the serum. The treated serum is incubated for 6-12 hours at 37°C. The serum is then separated through filtration from the crystal added, or from those formed during the incubation. The difference between the amount of cholesterol in the serum before and after incubation with the crystal, shows that while some sera increase their content in cholesterol through this treatment, others decrease it.

We could show that the serum of those rabbits which were fed with

two grams of cholesterol daily and which have a tendency to make atheromas, precipitates cholesterol. Oppositely, the resorption of atheromas seen in rabbits after the suppression of the feeding with cholesterol, was seen to occur together with the blood serum capacity to dissolve cholesterol. The relationship between this capacity to precipitate cholesterol and the appearance of atheromas was confirmed by the fact that it could not be seen in rats fed with cholesterol, where atheromas appear very seldom. Further it was seen present in subjects prone to make vascular occlusions. The administration of high amounts of cholesterol to animals with tumors has led to the appearance of vascular occlusions followed by ischemic infarcts in the tumors. The occlusion could be related to the proliferation of the arterial endothelium and the capacity to precipitate cholesterol.

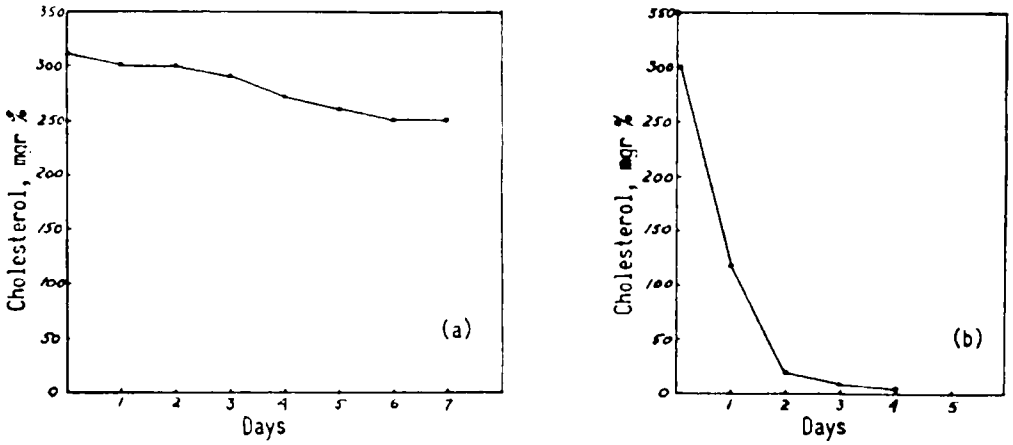


FIG. 152. The incubation of citrated blood at 37°C changes only little the amount of cholesterol in Case (a), while it determines a rapid decrease in Case (b).

In a further study of the cholesterol in blood, we investigated the capacity of the different samples of blood to cause their cholesterol to disappear after incubation at 37°C. We could show that while some samples of citrated blood kept at 37°C under sterile conditions, decrease their cholesterol content rapidly, others do not change it even after days of incubation. Figure 152 shows two such examples. We could also show that in rabbits fed with cholesterol and having atheromas, their blood lacked the capacity to make cholesterol disappear after incubation, differing from what was observed in the majority of the controls.

We then studied in another group of researches, the relationship between red cells and their cholesterol content. We could show that by washing red cells with saline, they lose their cholesterol. By using saline in amounts corresponding to the plasma, this effect could be measured. How-

ever, while in some bloods a manifest loss in cholesterol occurs with the first or second washing, in others the loss occurs very slowly. Sometimes ten such washings are necessary before the cholesterol is low enough to start hemolysis. Figure 153 illustrates two such examples. We could show that the red cells of rabbits fed with cholesterol demonstrated a higher capacity to retain cholesterol throughout saline washings, than did red cells of normal animals.

The analysis of arteriosclerotic cases from the point of view of this relationship between blood and cholesterol has shown that the tendency to precipitate cholesterol, coupled with a low capacity to make it disappear through incubation, is encountered in those cases prone to acute episodes of vascular occlusion.

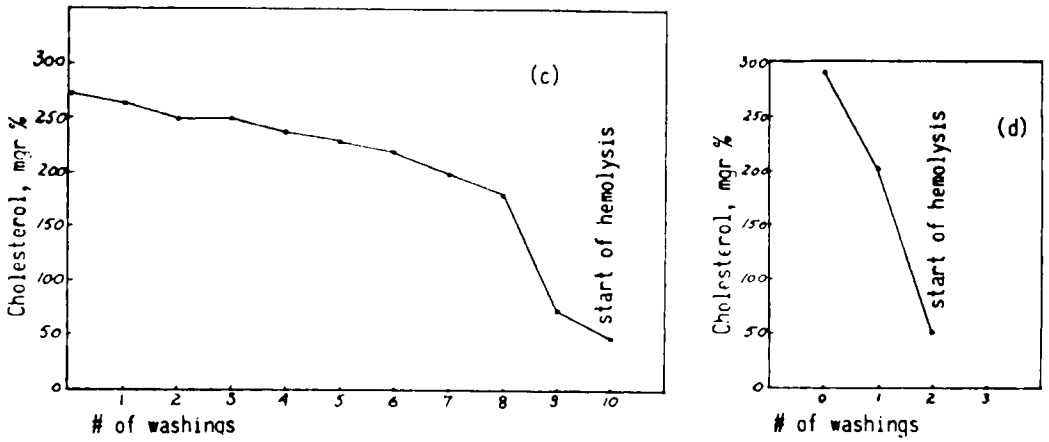


FIG. 153. The washing of human red cells with saline induces a very slow decrease in their content in cholesterol in Case (c). The hemolysis starts in this case at the 10th washing. In Case (d), such an effect appears after the second washing.

The big differences seen in the behavior of blood towards cholesterol has raised the problem of its relationship from an organizational point of view. The application of the concept of a *proper level* in the organization to cholesterol has permitted us to interpret the occurring changes.

Cholesterol represents a cellular constant and the classical studies of Shaffer have shown the importance of its amount in the cells. The quantity of water retained by the cells is largely determined by the ratio between cholesterol and fatty acids of the cells. Under this aspect, we have hypothetically considered hypercholesteremia as corresponding to a kind of defense response of the blood level toward the changes occurring at the level below it, respectively toward an opposite lipidic offbalance occurring at cells, tissues or even organs. We investigated hypercholesteremia under this specific

aspect. We have seen above that in the lipidic system, sterols correspond to an anti-fatty acid agent. This led to the supposition that hypercholesteremia could represent a response at the blood level to changes taking place at a lower level in the relationship between fatty acids and cholesterol. A first fundamental finding in this direction was the fact that the amount of cholesterol in the blood represents—as shown for potassium, copper, hydrogen ion concentration, etc.—values which, while maintained constant by a regulatory system, vary very widely under different circumstances. These wide variations would correspond rather to a secondary response. The amount of blood cholesterol would change as a secondary constant. A balanced system of manufacturing and excreting insures the maintenance of this secondary blood cholesterol amount. In the case of cholesterol, the manufacturing factor seems to be represented by the R E S cells, while the excreting factor by the liver, primarily by the Kuppfer cells and secondarily by the hepatic cells, the cholesterol being ultimately excreted in the bile. We do not know the factor which directly changes the manufacturing or excretion of cholesterol in blood and which consequently maintains its balance. By analogy we consider the changes in blood cholesterol value to result from those occurring at the lower levels as seen for other substances such as potassium, or copper, for which blood does not represent the proper level. According to this view, with cholesterol having the cellular level as its proper level and the blood as superior level, the blood changes would reflect secondary responses to those occurring at lower levels. We saw such changes at the cellular level in old age.

We could find thus that organs of old animals, perfused with saline to wash them from their blood, are richer in fatty acids and poorer in sterols than those of young individuals. The cellular lipidic abnormality, corresponding to aged persons, would correspond to a quantitative predominance of fatty acids. Their analysis showed that these fatty acids correspond qualitatively to those normally encountered in the organisms and especially to the polyunsaturated members. It should be noted at this time that this predominance differs from that found in abnormal conditions which corresponds to offbalance D. In this latter case, the fatty acids are abnormal.

With the concept that cholesterol belongs to the cellular level, we studied as we did for potassium *(See Chapter 5 Note 2)*, the concomitant changes in the amount of free cholesterol in plasma and in red cells. This was carried out to obtain information concerning the relationship between cholesterol and abnormal conditions. While a high or low amount in both plasmatic and cellular cholesterol would indicate an excess or lack of this substance, the discordance between these two data would correspond to

an offbalance. A high cellular, with a relatively normal or low plasmatic cholesterol, corresponds thus to an abnormal cholesterol offbalance predominant at the cellular level, while a relatively low cellular and high plasmatic cholesterol, to the opposite offbalance. By now considering cholesterol in its anti-fatty acid role, these changes permit further interpretation.

As we have seen above, cholesterol corresponds rather to the anti-fatty acid constituents controlling the normal polyunsaturated fatty acids and thus differs from the corticoids which represent agents opposing the abnormal fatty acids. The ultimate cause of hypercholesteremia would logically be sought in a quantitatively abnormally high amount of qualitatively normal fatty acids present at the lower levels.

Although hypercholesteremia represents by itself only a response to a fatty acid offbalance taking place at lower levels, the high amount of sterol present in blood can cause, by itself, a series of disagreeable manifestations. Hypercholesteremia can thus induce noxious manifestations although, teleologically speaking, it is directed to correct an offbalance at a lower level. The effect of this chronic richness in blood cholesterol is manifested in the circulatory system and atheromatosis appears as an immediate result. The precipitating tendency for any new increase in blood cholesterol explains the appearance of crystals in the cells of the intima and secondarily the appearance of atheromas.

Therapeutic Attempts

This pathogenic concept of arteriosclerosis presented above, has guided our therapeutic approach. As early as 1942, we used acid lipidic fractions of organs in a tentative therapy to control hypertension and indirectly arteriosclerosis, with interesting immediate results. We learned however, that not only were the effects temporary but also that after some time, the administration of unsaturated fatty acids induced a progressive increase in the amount of cholesterol present in blood.

The concept of hypercholesteremia as a secondary blood response to a cellular fatty acid predominance explained this occurrence and led us also to the further development of this approach. With cholesterol as an anti-fatty acid agent which appears in high amounts in blood, as a response to an excess of fatty acids at the cellular level, we tried to influence this secondary response by acting on the existing primary cellular offbalance. A decrease of this response could be obtained by supplying substances other than cholesterol, acting as anti-fatty acid agents. If the cellular fatty acid offbalance can be controlled, the organism as an entity would no longer be obliged to respond to the occurring offbalance and manufacture blood

cholesterol in excess. Without this need, hypercholesteremia will no longer appear. Under these conditions, the administration of anti-fatty acids has appeared as the logical way to prevent and even to combat an existing hypercholesteremia and its consequences.

Choice of the Anti-Fatty Acid Agent

The next problem was the choice of an adequate anti-fatty acid agent. It appeared advisable to use more than one such agent. One would intervene at the lower cellular level where the primary factor—predominance of fatty acids—exists; another would act at the level of the tissue and blood itself where their presence would act as an anti-fatty acid and prevent more directly the further appearance of cholesterol.

These considerations led us to utilize as active agents, heptanol, glycerol and polyunsaturated alcohols for the tissue level. Butanol was added, being more active at the organ and systemic levels. We found that mixtures of these alcohols were advisable also in view of the plurality of fatty acids intervening in this abnormal condition. Mixtures of polyunsaturated fatty alcohols were obtained through treatment with lithium aluminum hydride, of the fatty acids present in cod liver oil, fish oil, safflower oil, sesame oil, or even in the lipoacid fraction of organs.

Clinical Results

The best clinical results were obtained with a preparation having in its constitution, glycerol, polyunsaturated fatty alcohols, heptanol and butanol. In a series of subjects with persistent high amounts of cholesterol in blood, the administration of this preparation brought the blood cholesterol to low values. The following observations are characteristic.

Mr. M. R., 60 years old, had high cholesterol in the blood for ten years, with values above 350 mgr. %, in spite of severe diet poor in fats and cholesterol. Administration of unsaturated fatty acids brought the blood cholesterol, for a short time, to values between 260 mgr. and 300, returning to values above 350 after cessation of medication. Wtih the mixture—glycerol, polyunsaturated fatty alcohols, butanol and heptanol—the blood cholesterol went down to 150 mgr. % in less than two weeks without any side effects or restricted diet, and with a manifestly good general condition. It remained at this level for the 5 months of observation with only minimal and irregularly taken medication.

L. N., 70 years old, with blood cholesterol varying in recent years between 400 mgr. and 280 mgr. in spite of low fat and low cholesterol diet and different treatments. The mixture of glycerol, fatty alcohols, heptanol

and butanol, brought it down in three weeks to 160 mgr. It remained around this value for more than the six months of observation with no special diet and with only a very small amount of medication.

In a group of 20 subjects with cholesterol above 350 mgr. %, a descent of the cholesterol to values below 250 mgr. % was obtained in all the cases, with a treatment ranging from 10 days to 3 weeks. No inconveniences were observed.

Coronary Occlusion

The coronary occlusion with the consequent myocardial infarction represents the most important complications of arteriosclerosis. Death can occur instantaneously. In these cases it can be considered to result from a lesion of such localization or dimension as to be entirely incompatible with the function of the heart. When death occurs, not instantaneously but at any time after the occlusion has taken place, other factors have to be considered as intervening and leading to the fatal issue. Shock appears to be the most important one. Superacute shock, with death in a few minutes, an acute shock with death in 1-2 hours, or state of shock with death within hours or days, represent the other important intervening pathogenic factors added to the infarction itself. As seen above, these types of shock correspond to offbalances of the type D, this time with a predominance of abnormal lipoacids. A therapy with anti-fatty acid agents represents as shown above, the intervention which could prevent or reduce shock. While the administration of sterols appears contra-indicated, since it would increase the vascular occlusion, that of the non-sterolic anti-fatty acids is especially advisable.

The effect of these anti-fatty acid agents upon pain and the other symptoms which are of alkaline pattern, as well as upon the evolution of the condition, has fulfilled our expectations. We attributed an important role to glycerol in these cases. Its action similar to an anti-coagulant but limited to the level of the existing lesions, was able to prevent further local thrombosis without, however, the danger of a general reduction of blood coagulability. Administered in adequate amounts, guided by the pattern analyses, the mixture of the anti-fatty acid agents mentioned above has been followed by manifest clinical improvements.

L. K., 58 years old, with a history of several myocardial infarctions, was seen in a very severe state of shock. The electrocardiogram showed that besides the old lesion in the posterior wall, a new infarction of the anterior wall was present. Butanol was administered in doses of 5 cc. of the 6.5% solution together with 0.1 cc. glycerol every hour until the complete

cessation of symptoms and was continued 4 times a day afterward. The favorable effects continued in an unexpected form, the patient being without pain in less than 3 hours and without symptoms the third day. The cholesterol was found to be 135 mgr. % the fifth day.

This view of arteriosclerosis opens a new way for further research concerning many pathogenic problems, and a logical therapeutic intervention in this condition.