CHAPTER 4

DUALISM

As WE HAVE OBSERVED ABOVE, dualism prevails in nature. The concept of an oscillatory dynamic balance—the result of alternate operation of opposed forces—has been of special value in the study of most of the physiological phenomena. Over the years we have also constantly observed that in most physiopathological manifestations, dualistic patterns can be recognized. This dualistic pathogenic concept has helped to guide our study of disease. In cancer, it has permitted better understanding of many processes and manifestations. It has also served as a basis for our attempts to influence cancer and other conditions therapeutically. It was in the study of pain that, initially, we found clear evidence of pathogenic dualism.

PAIN

Many years ago, during experiments with an alcoholic extract of human placenta as a therapeutic agent in terminal cancer cases, a curious effect was observed. In some patients with painful lesions, administration of the preparation resulted in a decrease in the intensity of pain and even in its disappearance within a few minutes, with relief usually lasting for hours. In other cases, however, there was an opposite effect; pain increased in intensity within a few minutes after an injection. In some subjects, the exacerbation was so great and pain became so unbearable that the experimental treatment had to be discontinued quickly. In several cases in which the preparation was used in progressively larger doses, another noteworthy effect was observed: after the first injections, pain decreased and even disappeared for several days, only to have a new pain arise as treatment continued. This new pain became more intense after each injection so that the therapy had to be discontinued. Patients clearly recognized the difference between pains. The new one frequently had a burning character.

Thus, it became apparent that one substance could increase pain in some subjects and alleviate it in others, and could even alter the nature of the pain in the same subject. Pain, as demonstrated by antagonistic responses to a single agent, thus appeared to have a dual nature. Our immediate problem was to investigate this and its significance.

Physiological and Pathological Pain

In discussing the sensation of pain, most authors have found it necessary to distinguish between different types of pain. Some have classified pain as: 1) spontaneous, or 2) provoked, according to its mode of induction. Others have defined pain according to its site of origin and quality as: 1) superficial or cutaneous, and 2) deep visceral or somatic. Superficial pain from skin and mucous membranes near body orifices has been described as bright or burning in quality, while deep visceral or somatic pain arising from mesenchymal structures, certain mucous membranes and viscera has been described as diffuse and aching in quality. In many respects, attempts to define and classify pain in these terms have served to confuse rather than to clarify the problem.

That different types of pains do exist is an observation based upon common experience. For example, when a stimulus of sufficient intensity is applied to the skin for an adequate period of time, a sensation of pain is induced. This pain disappears rapidly when the stimulus is removed. But if the stimulus has been of such intensity and duration as to produce tissue damage, an after-pain may recur spontaneously some time after the stimulus has ceased. The original pain serves as a warning that the tissues are endangered. The after-pain, however, cannot be considered as a direct effect of the application of an external stimulus, but is rather a manifestation of true tissue damage.

As a first step, two categories of pain—one induced in normal tissue by external intervention, the other appearing as a pathological manifestation of an existing lesion—were established. We called the first, which is a normal sensorial sensation, "physiological" or "sensorial" pain. The second, a symptom of an abnormal local condition, was called "pathological" or "symptomatic" pain. This separation helped to eliminate discrepancies otherwise encountered in the study of pain, discrepancies which result when two entirely different manifestations, one sensorial and the other symptomatic, are studied under the same heading and investigated by the same methods.

Pain may be induced in damaged tissues by various stimuli not of sufficient intensity to arouse pain sensations in normal tissues. This sensitivity constitutes an abnormal response of tissues that have undergone pathological changes. Inflammatory, traumatic, circulatory, neoplastic or other pathological changes similarly may bring about either spontaneous pain or an abnormal degree of sensitivity of the involved tissues to external stimuli.

There are, therefore, two general types of pain which are biologically different. The first is a direct response of normal tissues to external stimuli which serves as a warning of danger. The organism reacts to this type of pain by seeking to run or to fight. The second type of pain arises as a consequence of tissue damage or disease to which the body responds by attempting to put the injured area at rest. This second type of pain, whether spontaneous or provoked, superficial or deep, is biologically different from the first pain experienced following the application of sufficiently intense external stimuli to normal tissues.

For purposes of further study, it would appear to be advantageous to distinguish between physiological or sensorial pain which is the response of normal tissues to noxious external stimuli, and pathological or symptomatic pain which is a manifestation of abnormal tissues. In the study of pain in all its aspects, it is necessary to keep this distinction in mind. While various investigative methods have furnished data concerning physiological pain, the information thus obtained is of very limited value when applied to the problem of pathological pain. However, it is pathological pain which constitutes the vital clinical problem, physiological pain being of concern in medicine primarily in the field of anaesthesia. *(Note 1)*

Dualism in Pathological Pain

It was only in pathological pain that a dual character was encountered. For one thing, it was noted that in some patients with chronic pain—associated with tumors, arthritis or other conditions—the pain intensity was not constant. In many of these patients, variations in pain intensity could be seen to follow a pattern. Although the variations usually are referred to as "spontaneous," we could show that they were related to the time of day. Furthermore, the variations were not the same for all patients. In one group, pain was severe in the morning and diminished toward evening, while in another group, little or no pain was felt in the morning and exacerbations occurred in the evening.

The intake of food also had a dual influence. In some patients with tumors far removed from the gastro-intestinal tract, pain was increased by eating while in others pain decreased. Patients themselves often recognized this relationship and many whose pain was increased with the intake of food refused to eat for fear of aggravating their suffering, while those of the other group wanted to eat whenever pain was severe in order to reduce its intensity.

These observations on the influence of time of day and intake of food on pain led to the study of the acid-base balance of the body since this balance is known to be influenced by the same two factors—time of day and food intake.

In a preliminary study we considered a special aspect of the acid-base balance of the body, that is, the several mechanisms involved and their possible intervention in the change of pain intensity. A study was made of blood pH, titrimetric alkalinity, CO_2 combining power, relative chloride distribution between erythrocytes and plasma, as well as urinary pH for the indications they furnish concerning the acid-base balance. The blood is highly buffered in order to avoid damage, through abnormal pH values, to cells in general and especially to those of the nervous system. Consequently, the variations in the blood pH are as limited as possible. Alkaline reserve and the chlorides repartition represent only part systems in the general acid-base balance. Titrimetric alkalinity, corresponding to the sum of ionized and nonionized constituents, furnish information of the broadest scale of the acid-base balance. Consequently it appears to be a highly significant measurement. Through the non-ionized constituents, it can vary greatly without influencing blood pH. It reflects thus otherwise hidden changes in the acid-base balance. We could show that alone, among all the variable factors of the blood acid-base balance, total titrimetric alkalinity of blood varies in parallel with the urinary pH. *(Note 2)*

As an immediate result of this research, it was possible to utilize the changes in the urinary pH as an indication of the most important variations occurring in the systemic acid-base balance. This makes it possible to use changes in the urinary pH as an indicator of the relationship between acid-base balance and variations in pain intensity.

Pain and Acid-Base Balance Changes

When changes in pathological pain intensity were studied in relation to changes of the urinary pH, a correlation could be established in the majority of cases. Two opposite kinds of relationship were observed when curves of the variations in pain intensity were compared with those of the urinary pH.

Patients who had experienced pain associated with chronic pathological lesions over prolonged periods of time were instructed to record carefully the relative intensity of their pain at regular intervals, such as every hour.

No analgesics were administered for at least six hours before or during the test period which was continued as long as possible, even for twenty-four hours. Patients were instructed to concentrate on a single painful area and to estimate the degree of pain intensity. They were told to consider an average degree of pain during each hour rather than momentary peaks during the observation period or the pain at the moment of recording. The

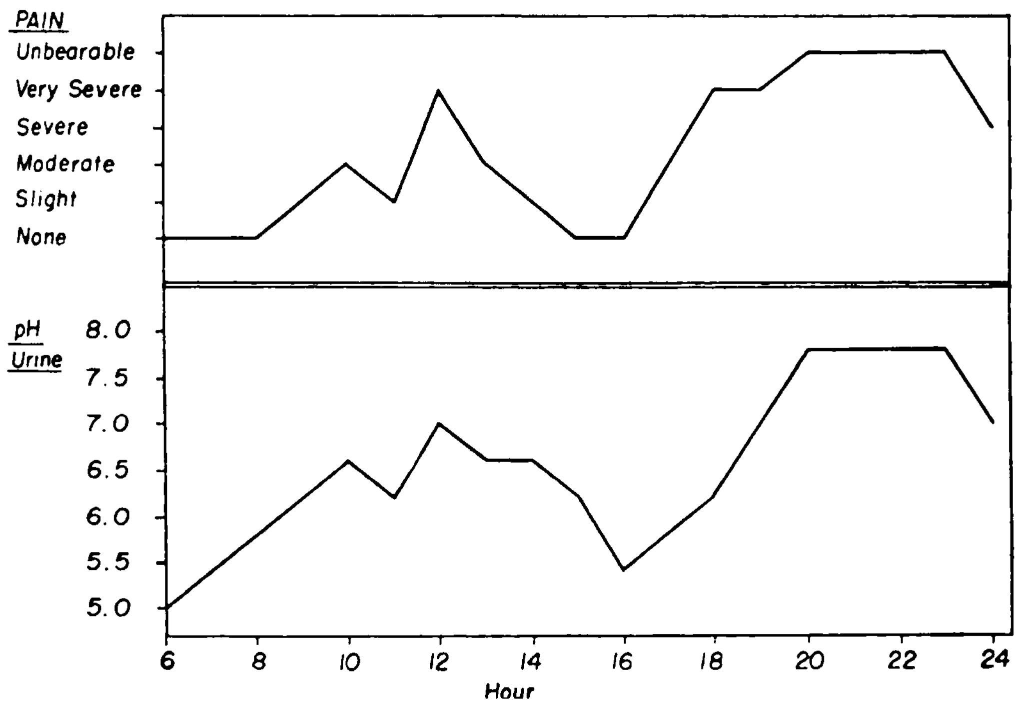

FIG. 6. *A pain pattern* is recognized by comparing the concomitant changes present in the curves of pain intensity with those of the urinary pH. The *parallel* variations of the two curves indicate an *alkaline pattern* with the pain more intensive when the urine is more alkaline, as seen in a case of carcinoma of the colon with painful abdominal mass.

degree was recorded in relative terms of no pain, slight, moderate, severe, very severe and unbearable, or as figures from 0 to 10.

Urine specimens were obtained each hour immediately after the pain intensity observations were recorded and the pH was determined electrometrically. Two curves—for the hourly variations in pain intensity and for urine pH—were then plotted.

Two distinct types of correlations were found. In the first, the two curves paralleled each other, the pain being more intense when the urine pH was higher, and less severe when the pH was lower. *(Figs. 6 and 7)* Because the maximal pain of this type of correlation is associated with a change toward alkalinity, this was called an alkaline pattern of pain.

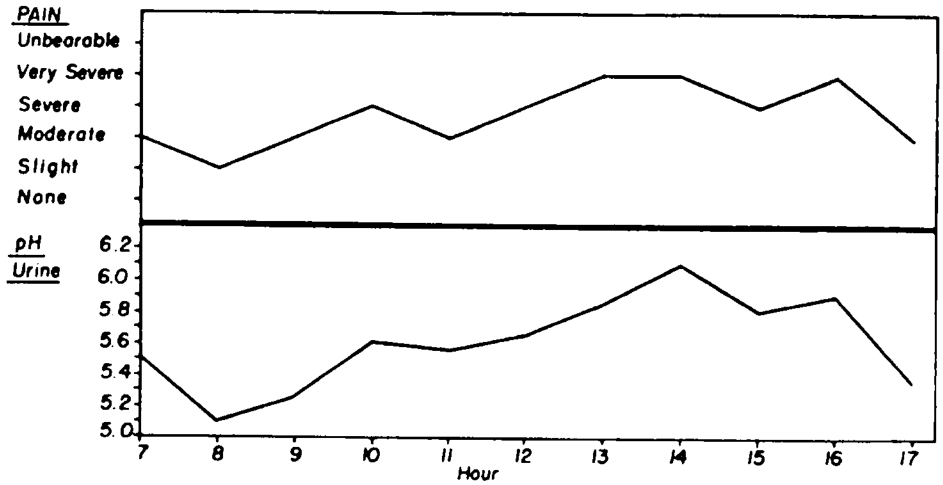

FIG. 7. *The alkaline pattern of pain* in which the concomitant variations in the curves of pain intensity and urinary pH are parallel, seen in a case of arthritis.

In the second type of correlation, the two curves varied inversely, pain being most marked when the urine was most acid, and least so when the urine was most alkaline. *(Figs. 8 and 9)* This second type was called acid pattern of pain because of its association with a change toward acidity. Considering the highly subjective nature of pain, the inconsistencies which occur are minor. Fig. 10 shows these curves followed during days.

The correlation between the pain intensity and urine pH curves are relative rather than absolute. The general level of urine pH apparently

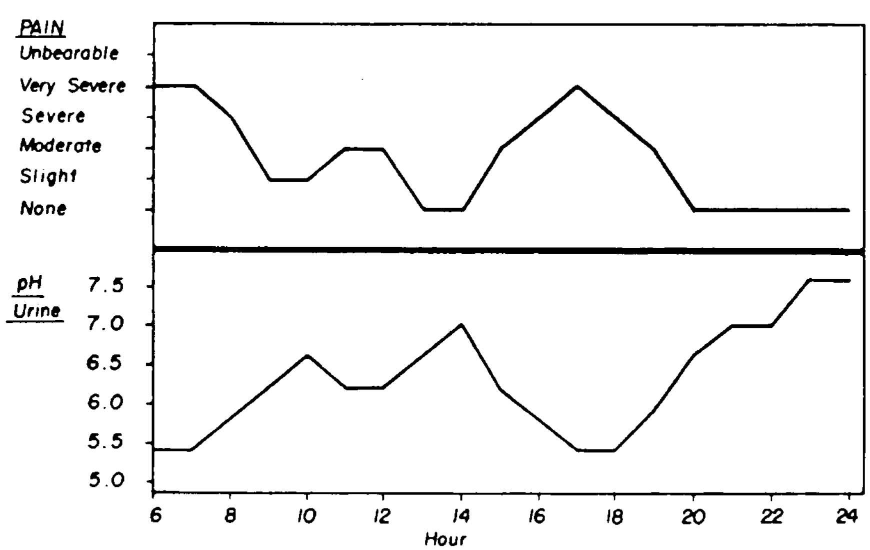

FIG. 8. *An acid pain pattern* is seen in a case of carcinoma of the prostate with metastatic bone lesions, in which the concomitant variations of the curves of pain intensity and urinary pH are divergent.

depends upon other factors. Consequently, only the fluctuations of the hydrogen ion concentration, rather than the absolute levels, are considered in this relationship to pain.

Changes in pain intensity were found to have a similar dualistic correlation with other factors as well as the acid-base balance—with potassium content of blood serum, for example. Studies were made to compare the concomitant changes in pain intensity and in potassium content of blood serum. In several cases the acid and alkaline patterns of these pains were determined through the relationship to urinary pH variations. At different

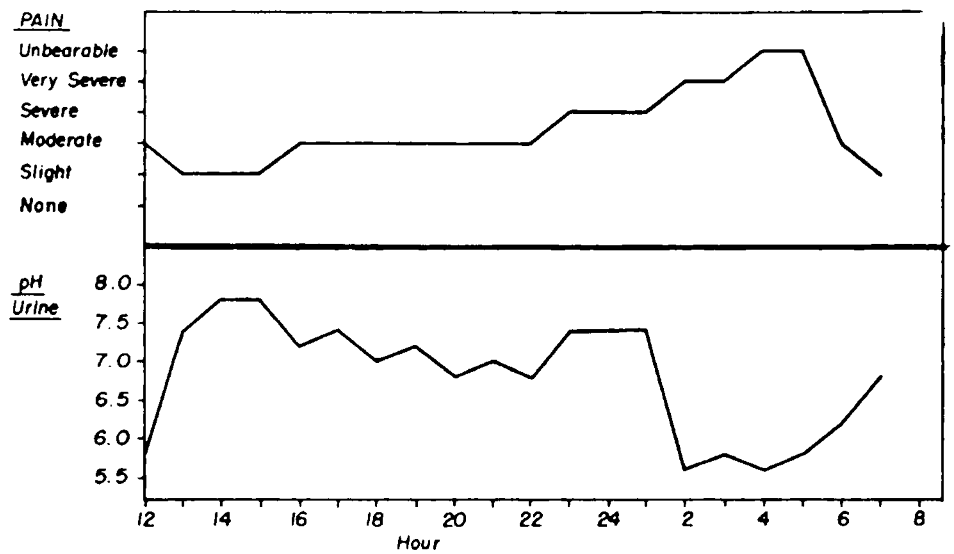

FIG. 9. *An acid pattern of pain* recognized by the divergent variations of the curves of pain intensity and urinary pH is seen in a case of phantom limb.

moments, especially when the pain was markedly different in intensity, blood was obtained by finger puncture, and collected in glass capillaries. After clotting, the serum was immediately separated and the potassium content measured using a flame photometer. Curves of the values of pain intensity at these moments, established by the method previously mentioned, and of the concomitant K^+ content were compared. Figs. 11 and 12 show the two curves in two cases in which, the two pain patterns—acid and alkaline, were primarily recognized. The cases with high serum potassium values and with parallel changes between the two curves—pain intensity and K^+ content—were seen to correspond to alkaline pain pattern; the other cases with less serum potassium and opposite variations of the two curves were seen to correspond to the acid pain pattern.

We extended the study of the pain pattern, as revealed by concomitant variations of pain intensity and body acid-base balance, from cancer cases, in which a frank dualism had been seen, to other painful conditions. It was interesting to note that, in many conditions, pain can have one or the other pattern but there are some conditions in which only one pattern is consistently found. Pain following trauma of any kind—the pain of post-

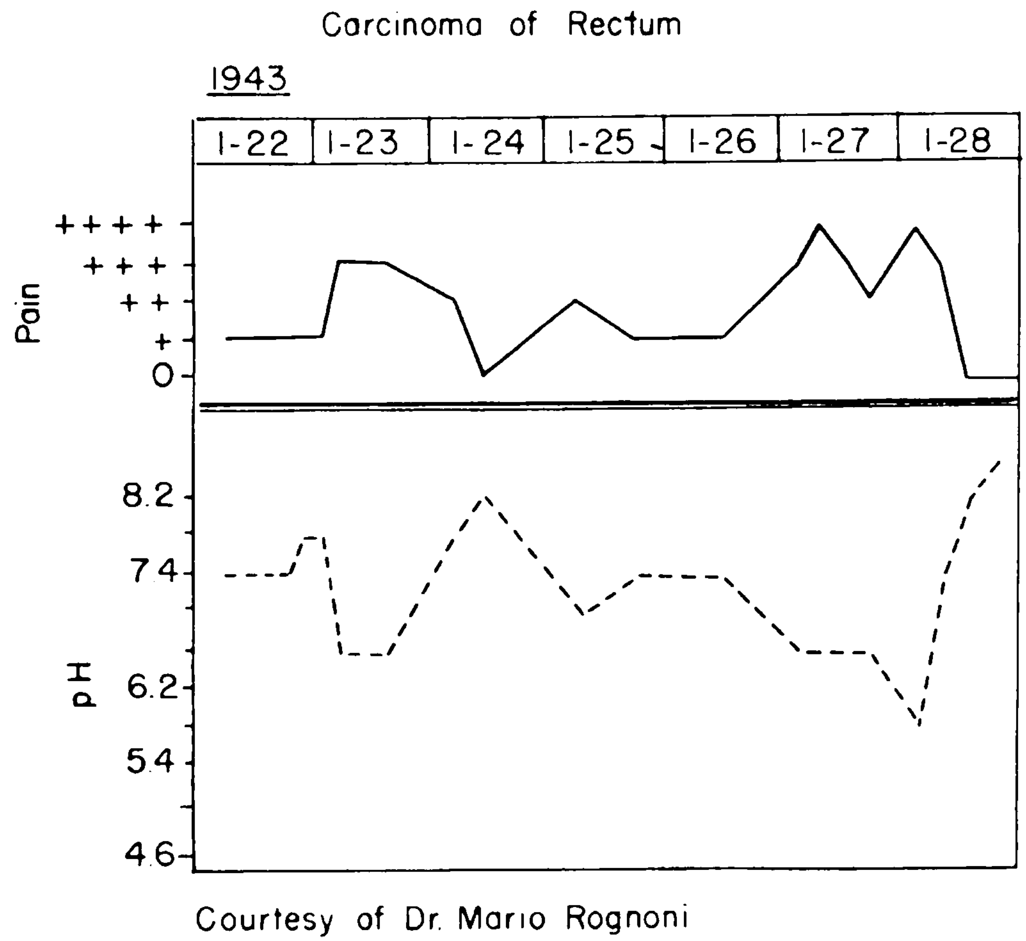

FIG. 10. The *pain pattern* can be recognized also through the characteristic opposite variations of the curves of pain intensity and urinary pH, followed during successive days—instead of hours—as seen in the above curves of a case of cancer of the rectum. (Courtesy of Dr. Rognoni)

operative and accidental wounds, burns and fractures, for example—always has an alkaline pattern. This is also true for the pain of gallbladder colic. In other conditions, either pattern may be present and must be determined by analysis. For instance, the pain of neuritis and simple headache has an acid pattern in some cases, alkaline in others.

In rheumatoid arthritis, an alkaline pain is almost constantly found. In osteoarthritis, the pain is of an acid type. In arthritic patients in whom this relationship did not seem to hold, it was possible to recognize not only the existence of both rheumatoid and osteoarthritis but also to note that the pain pattern, as shown by test, was related to the more painful condition. We utilized the diagnosis of the type of pain present as an indication of the nature of painful processes. We will see later how this correlation has been confirmed by therapeutic trials.

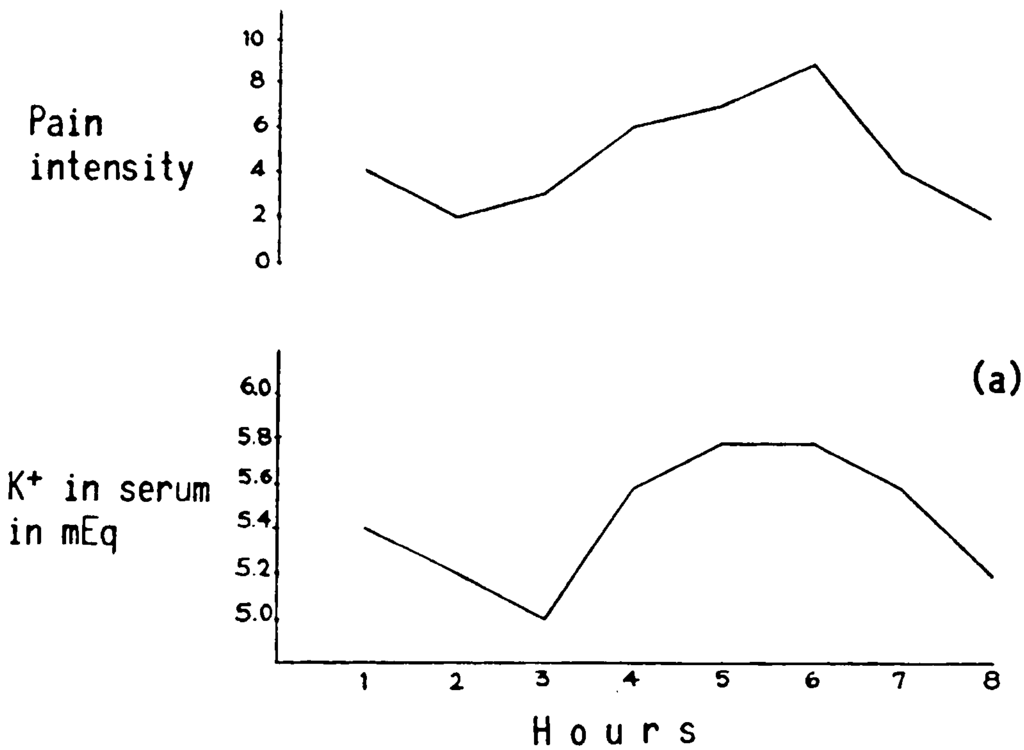

FIG. 11. *Pain pattern and potassium in blood serum.* The comparison of the concomitant changes in the curves of pain intensity and those of the amount of potassium in blood serum shows parallel variations in a case with an alkaline pattern.

Two types of pain associated with two different conditions present in the same individual have been found to occur more frequently than expected, although usually not simultaneously active.

In most patients with two or more anatomically separated painful foci, parallel variations occurred between the curves of the different pains. Only in occasional cases were the two pains found to vary simultaneously but in opposite fashion. Their opposite patterns were well described by patients who observed "the two pains act as if they were part of a balance; when one goes up, the other goes down, and the opposite." In Figure 13, the pain curve of lesion A is seen to vary inversely with the curve of urinary pH, while the pain curve of lesion B is parallel with the urinary pH curve. Thus,

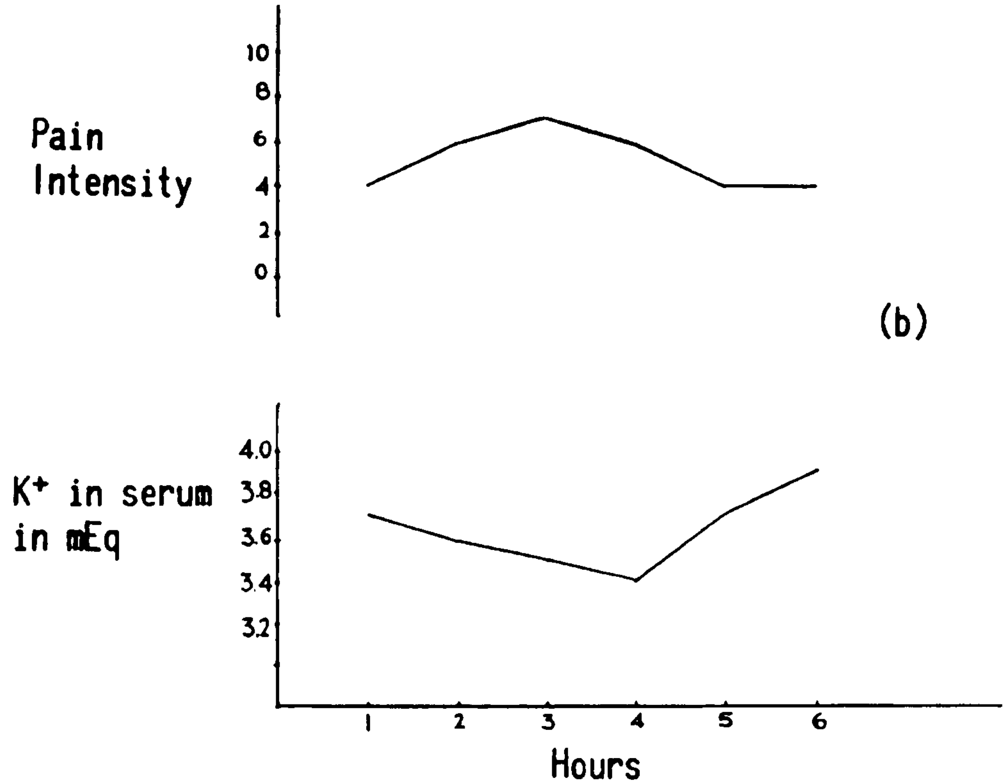

FIG. 12. Divergent variations between pain intensity changes and those of the blood serum potassium in a case of acid pain pattern.

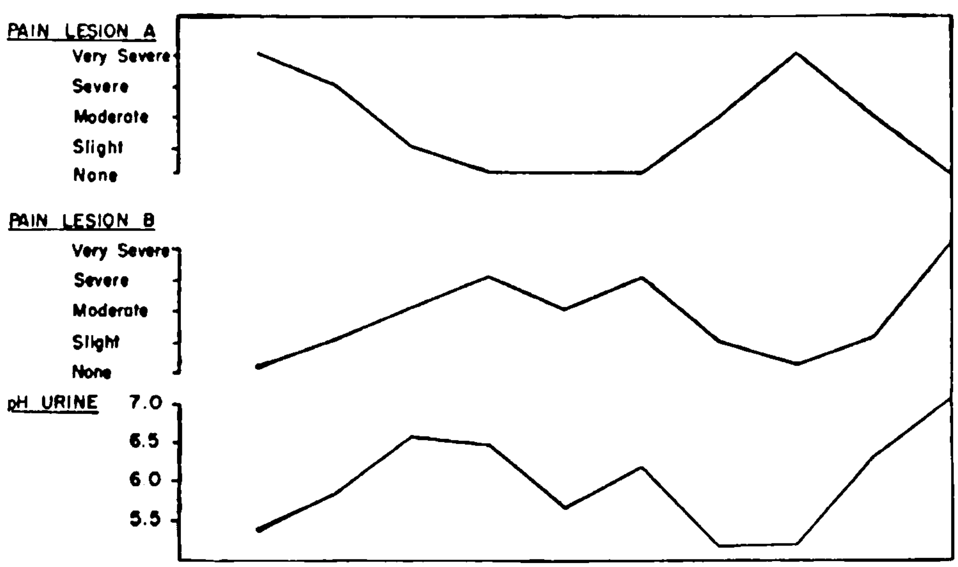

FIG. 13. *Pains.* Acid and alkaline pains can co-exist on different lesions, as seen in a patient with multiple osseous metastases from breast carcinoma. Lesion A, which corresponds to an acid pattern, shows divergent variations between the curve of urinary pH and that of its pain intensity, while for lesion B, with an alkaline pattern, the variations of the curves of pain intensity and of urinary pH are parallel.

the pain of lesion A is of an acid pattern while that of lesion B is of alkaline pattern.

Also interesting to note is the persistence of the same pattern for pains associated with chronic conditions. We have headache patients, for example, in whom, during the 20 years since we first determined the pattern of pain, there has been no changes of pattern. In others, on the contrary,

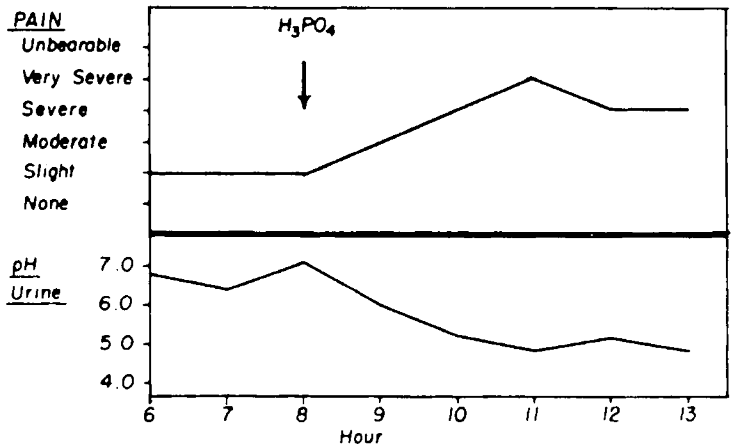

FIG. 14. The changes induced in the pain intensity by the administration of an acidifying agent indicate the pattern present. Pain with an *acid pattern* is intensified following oral administration of 1.5 cc. of a 50% sol. of phosphoric acid. Urinary pH changes reflect the induced systemic acidification.

changes occur rapidly. In a case of sciatica, we have seen rapid and frequent changes in pattern, especially in response to therapeutic measures.

Worthy of being noted is the correlation found between variations in pain intensity and changes in the acid-base balance of the body even in cases in which nerves are directly involved in lesions and in which a mechanical pathogenesis usually has been accepted. This would indicate that the chemical factor mentioned above has a role in the pathogenesis of pain even in these cases.

Acidifying and Alkalizing Agents

We next demonstrated the cause-effect correlation between acid-base changes and variations in the intensity of pain. Administration of acidifying or alkalizing substances could induce the same changes in pain intensity as those caused by spontaneous variations in the acid-base balance of the body.

The relationship between acid-base balance changes and pain intensity was thus investigated by administering strong acidifying and alkalizing agents to patients after the type of pain-urinary pH correlation had been determined. Administered orally, strong acidifying substances, such as phosphoric acid, ammonium chloride or mono ammonium phosphate, increased the severity of pain with an acid pattern, *(Fig. 14)* and reduced the severity of one with an alkaline pattern. *(Fig. 15)* At the same time, it caused a lowering of the urine pH.

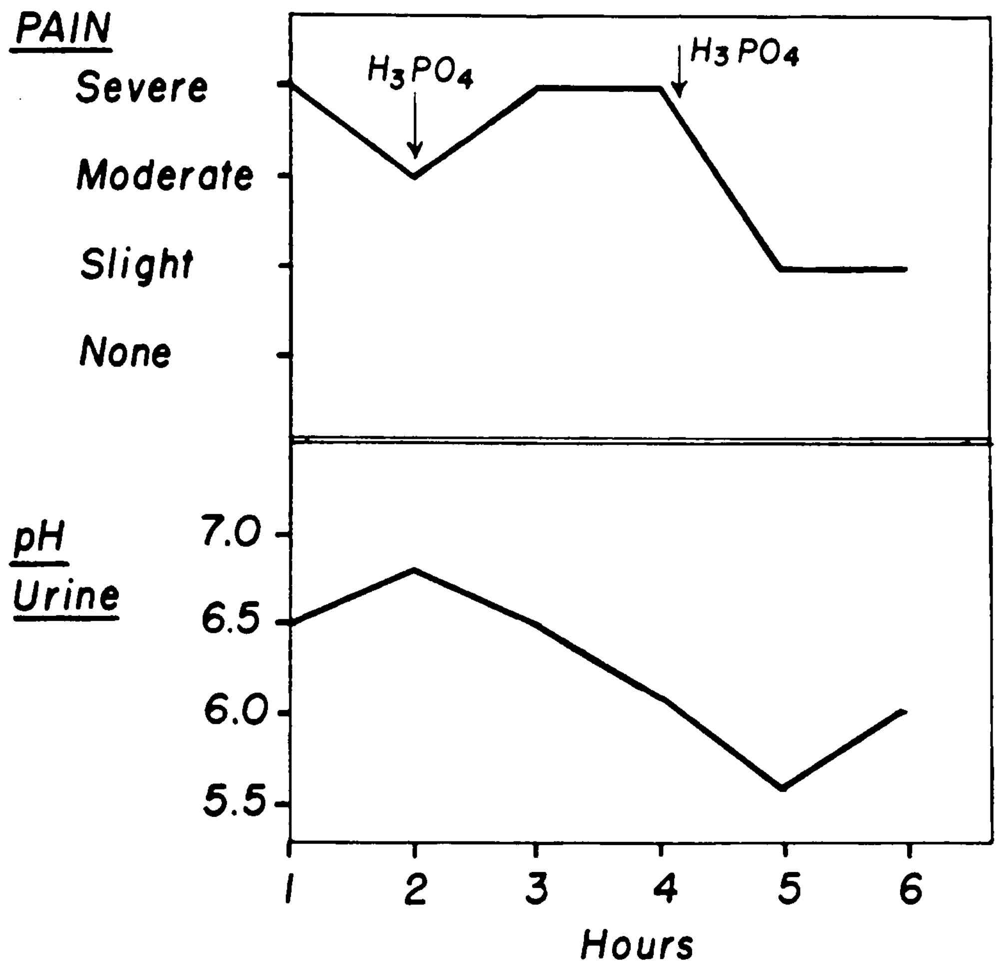

FIG. 15. Pain with an *alkaline pattern* is relieved by oral administration of two doses of 1.5 cc phosphoric acid (50% sol.). Urinary pH changes reflect the systemic acidification.

Sodium bicarbonate or ammonium acetate in quantities that alkalinized the urine increased intensity of pain with an alkaline *(Fig. 16)* and diminished intensity of pain with an acid pattern. *(Fig. 17)*

These changes of the systemic acid-base balance induced by administration of strong acidifying or alkalizing agents explains how similar changes, when they occur spontaneously, affect pain intensity. The effect

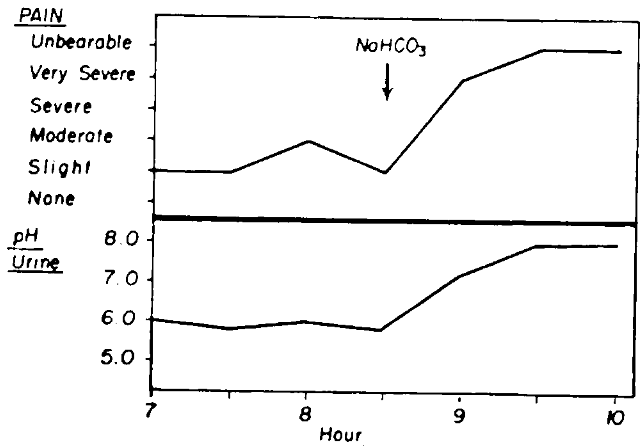

FIG. 16. Pain with an *alkaline pattern* is intensified by oral administration of 5 grams of sodium bicarbonate. Urinary pH changes reflect the systemic alkalinization.

may be to increase or decrease the intensity, depending upon the pattern of the existing pain. It is interesting to mention that similar changes of the systemic acid-base balance, spontaneous or induced by the administration of acidifying or alkalizing agents, do not influence either the threshold or intensity of physiological pain. We have often utilized this response to alkalizing or acidifying substances as a method of recognizing the acid or alkaline pattern of pain. *(Fig. 18 bis)*

Dualism in Local pH Measurements

Since it had been observed that a definite correlation exists between the variations in pain intensity of abnormal foci and changes in the gen-

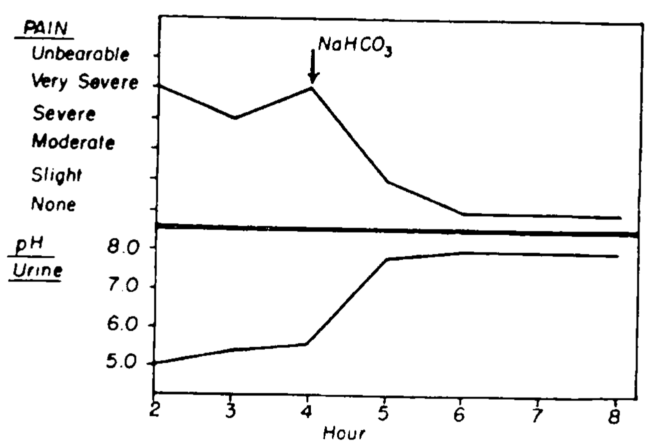

FIG. 17. Pain with an *acid pattern* is relieved by oral administration of 5 grams of sodium bicarbonate. Urinary pH changes reflect the systemic alkalinization.

eral reaction of the body, it was desirable to ascertain what changes were taking place within the abnormal foci themselves at the same time.

Patients with easily accessible superficial lesions, especially tumors, in which painful areas could be well localized, were employed in these experiments. The pattern of pain, acid or alkaline, was first determined in the manner previously described. Local pH determinations were then per-

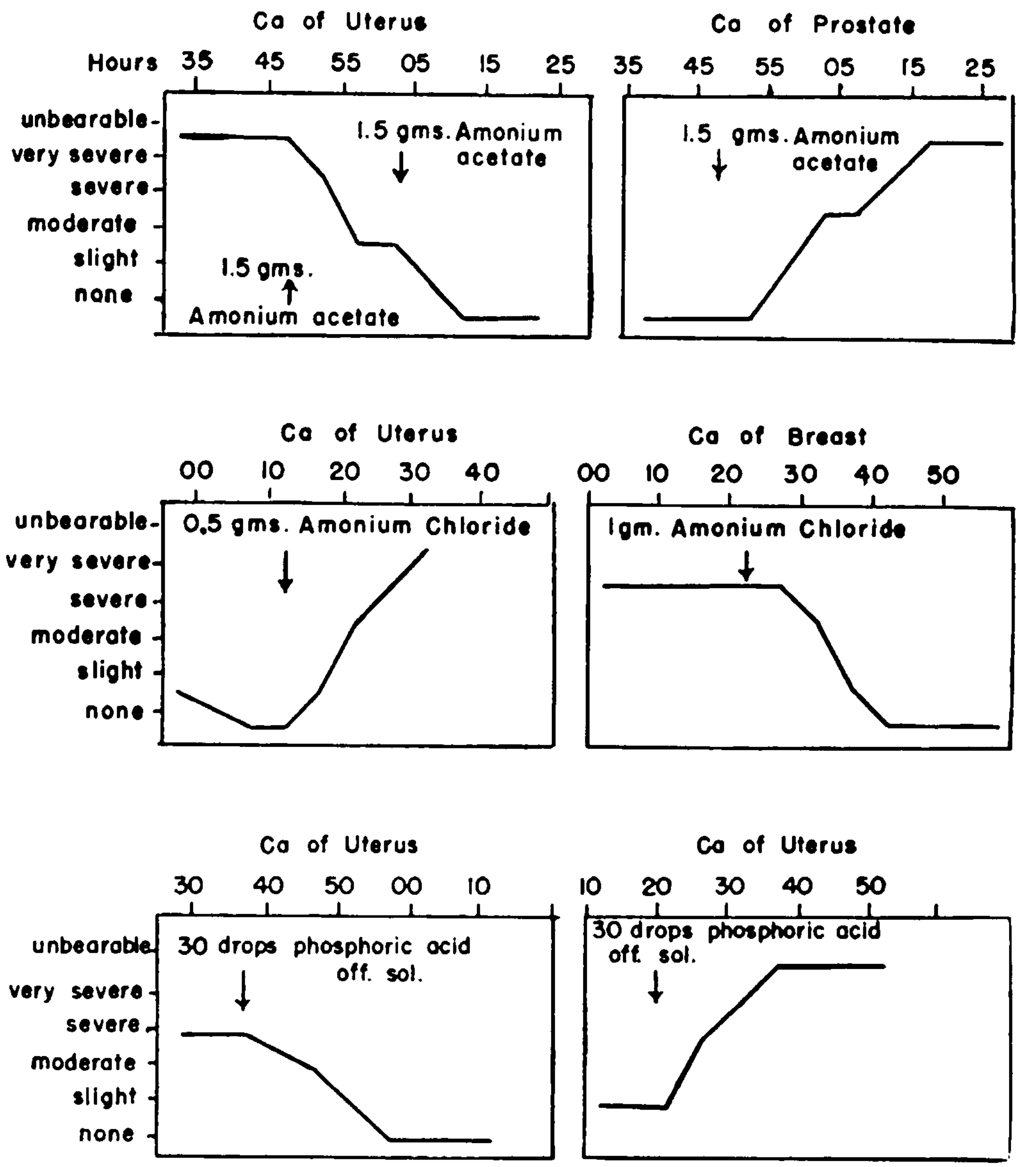

FIG. 18bis. The response of the pain of a lesion to an agent permits to identify the acid or alkaline pattern present. The effect of an acidifying and alkalizing agent corresponds to an increase or a decrease in pain intensity, according to the pain pattern present. First row, left side—acid pattern, right side—alkaline; second row, left side—acid, right side—alkaline; third row, right side—alkaline, left side—acid pattern.

formed. Special glass electrodes* were used for this purpose and determinations were carried out employing a sensitive pH meter. The tip of the electrode was placed on the surface of the area to be tested if ulcerated, or was introduced into the tissue to be tested through a small incision. In reality this gives a measurement of the pH of the local interstitial fluid.

Urine pH and local pH determinations were then performed at different times corresponding with spontaneous variations in the pain intensity experienced by the patient. Simultaneously, the pH values of normal tissue areas and, when possible, of nonpainful tumor areas were determined. Similar studies were carried out after administration of strong acidifying and alkalizing agents.

Many difficulties were encountered both in the choice of suitable clinical subjects and in techniques. Neoplasms proved to be the simplest type of painful abnormal process to employ. The neoplasm had to be located in a readily accessible region so that the electrodes could be introduced into an ulcerated area or through small incisions. The patient had to be able to very accurately localize the area of pain since considerable differences in pH values were found to exist in different parts of the same lesion. The pain had to be superficially localized because accurate determinations in the depths were not possible. Finally, the complete cooperation of the patient was essential.

The data obtained for a patient with an ulcerated, profusely draining carcinoma of the breast is recorded in TABLE II. Pain was most intense

TABLE II

OBSERVATIONS IN A CASE WITH ALKALINE PAIN PATTERN

Treatment (oral)	Pain Intensity	pH Urine	pH Normal Tissues	pH Tumor
	None	5.4	7.3	7.6
	Moderate	6.2		8.1
	Very severe	7.1	7.4	8.5
Phosphoric acid 50%, 2 cc.	Slight	5.5	7.3	7.9
Sodium bicarbonate 5 grams	Unbearable	7.8	7.4	8.8

when the acid-base balance of the blood, as reflected in the urine pH changes, was relatively most alkaline, and was less intense when the balance was more acid. The pH values of the painful areas of the tumor in

* Supplied by Hartman and Braun, Paris.

this case showed considerable lability under the influence of spontaneous changes in the general acid-base balance of the body, reaching a high of 8.5. At this time, the pain was very severe. The pain became unbearable following oral administration of 5 grams of sodium bicarbonate, and the pH within the same tumor area reached 8.8. The pH of the normal tissues in this case, even after the administration of strong alkalizing agents, never exceeded 7.4, while the tumor pH was never below 7.6.

The findings in a case with acid pain are recorded in TABLE III. This

TABLE III

OBSERVATIONS IN A CASE WITH ACID PAIN PATTERN

Treatment (oral)	Pain Intensity	pH Urine	pH Normal Tissues	pH TUMOR Painful area	pH TUMOR Nonpainful area
	None	7.0	7.4	6.8	7.2
	Moderate	5.8		6.3	7.1
	Severe	5.3	7.3	5.8	6.9
Phosphoric acid 50%, 1.5 cc.	Unbearable	5.0	7.3	5.5	6.8
Sodium bicarbonate 5 grams	None	7.4		6.6	7.2

patient had an extensive sarcoma of the face which was not ulcerated but involved the skin. Pain was most intense when the blood titrimetric alkalinity was relatively low and less severe when the alkalinity was higher. The pH values in the tissues of a painful area of the tumor were always more acid than the values found in another nonpainful area. The pH of the nonpainful area was slightly below that within normal tissues. Spontaneous changes in the acid-base balance of the body brought about a reduction of the pH of the painful tumor area to 5.8, at which time the patient reported severe pain. The nonpainful tumor area had a pH of 6.9 at the same time. Following administration of 1.5 cc. of 50% phosphoric acid, pain became unbearable and the pH within the tumor tissues of the painful area fell at once to 5.5. At the same time, the nonpainful tumor area pH was 6.8 and the normal tissue pH was 7.3.

Similar results were obtained in other cases and led to the following conclusions: The pH values of the interstitial fluid of painful lesions studied in vivo differ from those of normal tissues, the hydrogen ion concentration being either higher or lower than that of normal tissues of the same individual. The pH of painful abnormal tissues is much more labile and extremely sensitive to general body pH changes. Spontaneous or induced variations in the acid-base balance of the body produce slight changes or none at all in the pH of the interstitial fluid in normal tissues, but give rise to more pronounced changes of the pH within painful pathological tissues.

Through this research, we have thus been able to connect pathological pain to the pH of interstitial fluid of painful lesions. A further connection could be made with the richness of the interstitial fluids in potassium. In the alkaline pattern of pain, more potassium was found in the interstitial fluids. The presence in these fluids of potassium—the cation of the cytoplasma—in higher amounts than in normal conditions was seen to induce pain. The subcutaneous administration of potassium compounds was seen to be painful, while similar salts of sodium were well tolerated. As a local acidosis was found in lesions having an acid pain pattern, a local alkalosis and an increase in potassium content appeared in those with an alkaline pain pattern. The intensity of pain in this case was found to be proportionate to the degree of abnormal deviation of the local pH and to the abnormal amounts of potassium in the interstitial fluids. In addition to variations in the acid-base balance of the body, variations in the amount of serum potassium appear able to alter pain intensity in cases with an alkaline pattern. This correlation is further explained below by the place of potassium in the organization.

Oxido-reduction Potential

Differences indicating the same dualism were also found in other manifestations in painful lesions. The oxido-reduction potential was measured in tumors with pain. Patients chosen were those with easily accessible superficial tumors in which painful areas could be localized. Platinum needle electrodes were introduced in the painful areas through small incisions or, if the lesions were ulcerated in the lesions themselves. The measurements of the potential present were made using a Beckman pH meter. As had been the case for the pH, it appeared important that the patient be able to indicate clearly the painful areas. Because exact location of these areas in the depths was almost impossible, superficial lesions usually were chosen for these determinations. In general, in lesions with an alkaline pattern, the measurements showed high values (such as from +100 to +350 millivolts) while in lesions with pain of the acid pattern, the values were low (such as −2 to −15 millivolts).

Abnormal Substances

Changes in the local pH, like changes in acid and alkaline patterns, could be related to the appearance and subsequent accumulation of different substances in the lesion. Increased concentration of lactic acid was found in the interstitial fluids of acid pattern lesions, while increased concentrations of sodium and especially potassium ions were found in the interstitial fluid of lesions with an alkaline pattern.

Processes leading to a local acidosis are known and ascribed to the well-known anoxybiotic metabolism of carbohydrates. They result from lack of the "respiratory" oxybiotic phase of carbohydrate metabolism, with the consequent conversion of pyruvic acid into lactic acid. Only part of the lactic acid is changed into glycogen through the Pasteur-Myerhoff reaction, and an accumulation of lactic acid results. While the presence of lactic acid is well known, its presence has not previously been related to pain or other manifestations. We could show this correlation in some cases. *(Note 3)*

The scientific literature offered no information concerning the appearance of alkaline compounds. We were able to establish that the presence of sodium ions coincides with another anomaly found in these lesions—a high fixation of chlorides in the lesions themselves. Values of 1600 mgr. of Cl., or even higher, per 100 gms. of wet tissue were found in these lesions instead of about 400 mgr./100 gms. measured in normal tissues. The local alkalosis and the resulting alkaline pain pattern could thus be correlated with an abnormal sodium chloride metabolism at the tissular level in which with chloride ions fixed by the cells, sodium ions remain free to combine with carbonate anions and form alkaline compounds. If the abnormal NaCl metabolism occurs in the interstitial fluid, the subsequent alkalosis induces pain. We will see later how abnormal NaCl metabolism also takes place at other levels of the organization. In these cases of alkaline pattern of pain, the fact that abnormal amounts of sodium ions still enter the cells will result in a loss by these cells of potassium which will accumulate in the pericellular fluids, and form alkaline compounds.

An immediate conclusion that could be drawn from these studies was that there is a definite dualism in pathogenesis of pain originating in abnormal tissues and that the two pain patterns evidenced in lesions with acidosis or alkalosis of the interstitial fluids indicate that processes of two opposite natures go on at the tissular level.

OTHER ACID AND ALKALINE SYMPTOMS

Using the same method of investigation as in the study of pain, a relationship between variations in intensity of certain other symptoms and variations in urinary pH could be found. Acid and alkaline patterns of itching could be recognized. The same patterns could be found for vertigo and impaired hearing. Among psychiatric manifestations, manic-depressive states showed changes that could be related to acid-base variations.

The correlation between dyspnea and acid-base variations was contrary to what we expected. Classically, dyspnea is believed to be associated only with an increase of acidity of blood. However, both acid and alkaline patterns of dyspnea were observed, and could be related more directly to changes at the tissue level. We will review here the pathogenesis of itching, vertigo, dyspnea, and other conditions, under this dualistic aspect.

Itching

The problem of itching is interesting from other than the therapeutic point of view, since little is known regarding the nature and cause of this condition. Various hypotheses have been offered but have failed to explain its pathogenesis. Our interest in itching originated during the study of pain and led to an hypothesis which allows us to approach the problem from a new angle. By analogy with pain, we separated itching into two types: physiological, as the response of normal tissues to external stimuli; and pathological, as a sensation arising within diseased or damaged tissues. Tickling the normal skin or even stimulating it through heat, cold, etc., may cause a sensation of itching and lead to scratching. Certain mucous membranes, such as those of the nose, and the skin around natural orifices, are especially sensitive to such stimulation. This type of itching, as a response of normal tissues is *physiological or sensorial.*

Under pathological conditions however, the skin, mucous membranes and other formations may itch without external stimulation or in response to stimuli which ordinarily do not produce this sensation. The itching then can be considered as a manifestation of diseased or damaged tissues and, as such can be described as *pathological.* Just as does pathological pain, pathological itching represents a symptom related to abnormal changes already present. *(Note 4)*

In spite of their relative independence, the fact that similar fundamental mechanisms are involved in the production of itching and pain explains certain characteristics they have in common. Like pathological pain, pathological itching varies in intensity with the time of day. Patients with chronic pruritus are aware of this. Some have more itching in the morning, others experience exacerbations at night. The same dualism is seen with intake of food. For these reasons, the relationship between changes in acid-base balance of the body, as reflected in the urinary pH, and variations in intensity of itching was investigated.

Patients with long standing pruritus associated with a variety of chronic skin conditions were studied. They were asked to note over periods of six to twelve hours the changes in itching intensity. Evaluation of the changes was made by the patients themselves, using a series of qualifications such as none, slight, moderate, severe, very severe and unbearable, or a scale ranging from 0 to 10. They were instructed to consider the average inten-

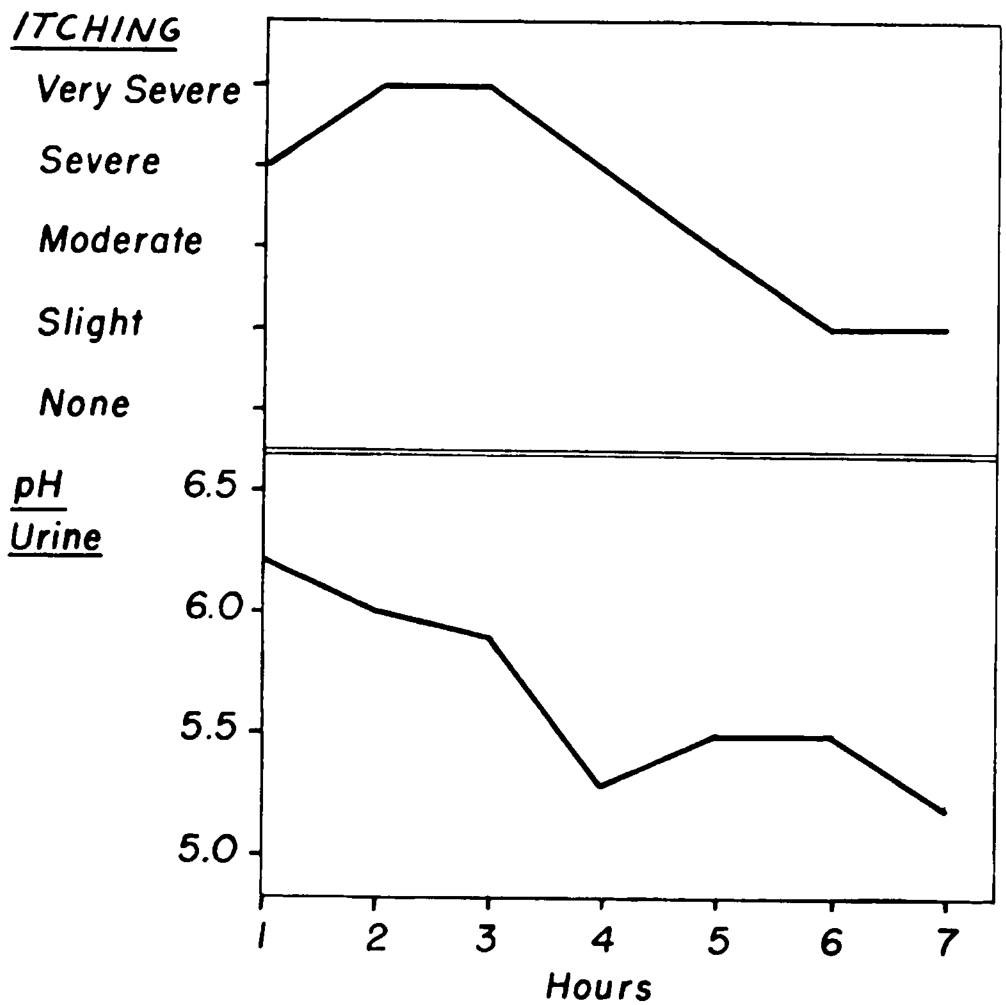

Fig. 20. *The alkaline pattern of itching* is recognized in a case of senile vulvar pruritus, through parallel variations of the curves of the intensity of the *itching* and of the urinary pH.

sity of their itching for each hour, rather than to indicate the maximum intensity at the exact time of recording. Voided urine specimens were obtained at the end of each hour. The pH of the urine specimens was determined electrometrically. A graph was plotted to compare the variations in the subjective data furnished by the patient with the concomitant hourly changes in the pH of the urine. It was usually necessary to repeat the test several times before the patient appeared able to satisfactorily evaluate the changes in the intensity of the symptom for hour-long periods rather than

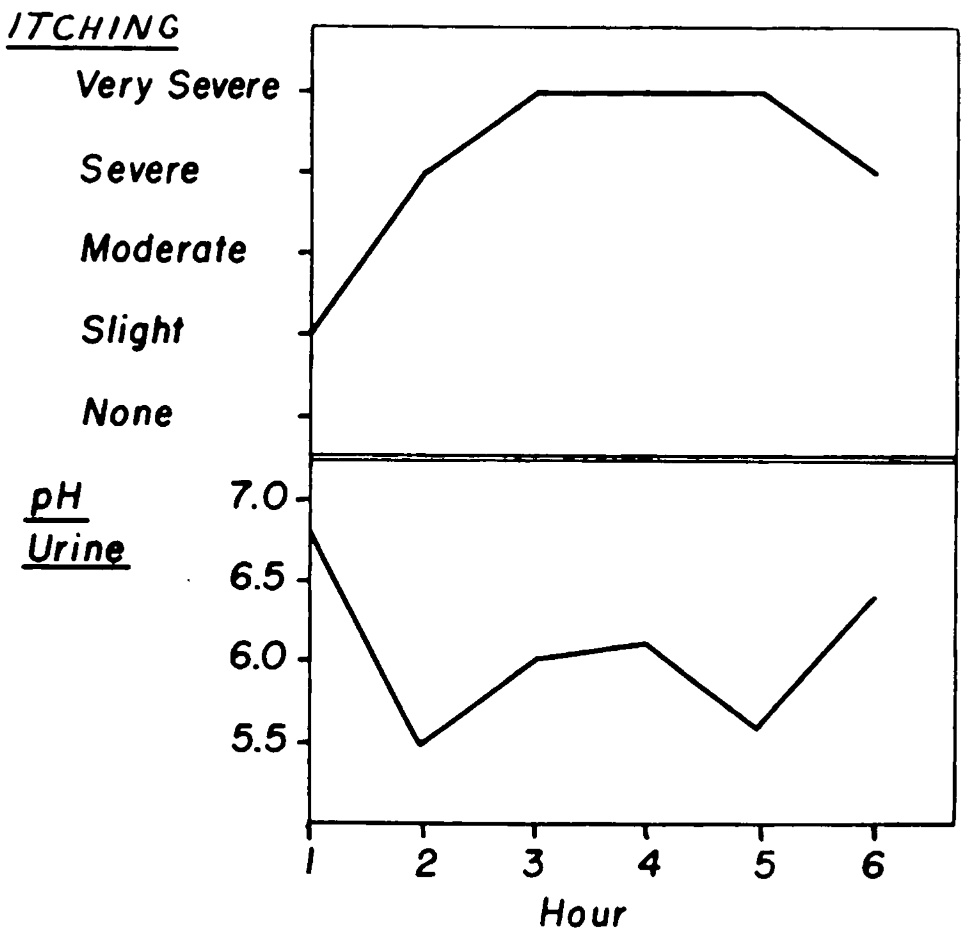

FIG. 21. *An acid pattern of itching* is recognized in a case of pruritus ani through the divergence in the concomitant variations of the curves of itching intensity and urinary pH.

for just the moment of recording. (We also tried to judge the intensity of itching through the frequency, intensity and duration of scratching, as noted by an observer, but without success.) Fifteen patients were studied and, because of the limited number, the results are presented as merely preliminary.

In four cases, the curves of itching and urinary pH did not show any definite correlation even after repeated tests. Of the remaining 11 cases, 7 showed a distinct parallelism of the two curves, and in the other 4, an inverse relationship between curves was apparent. The graphs obtained in two characteristic cases are presented here. *(Figs. 20 and 21)*

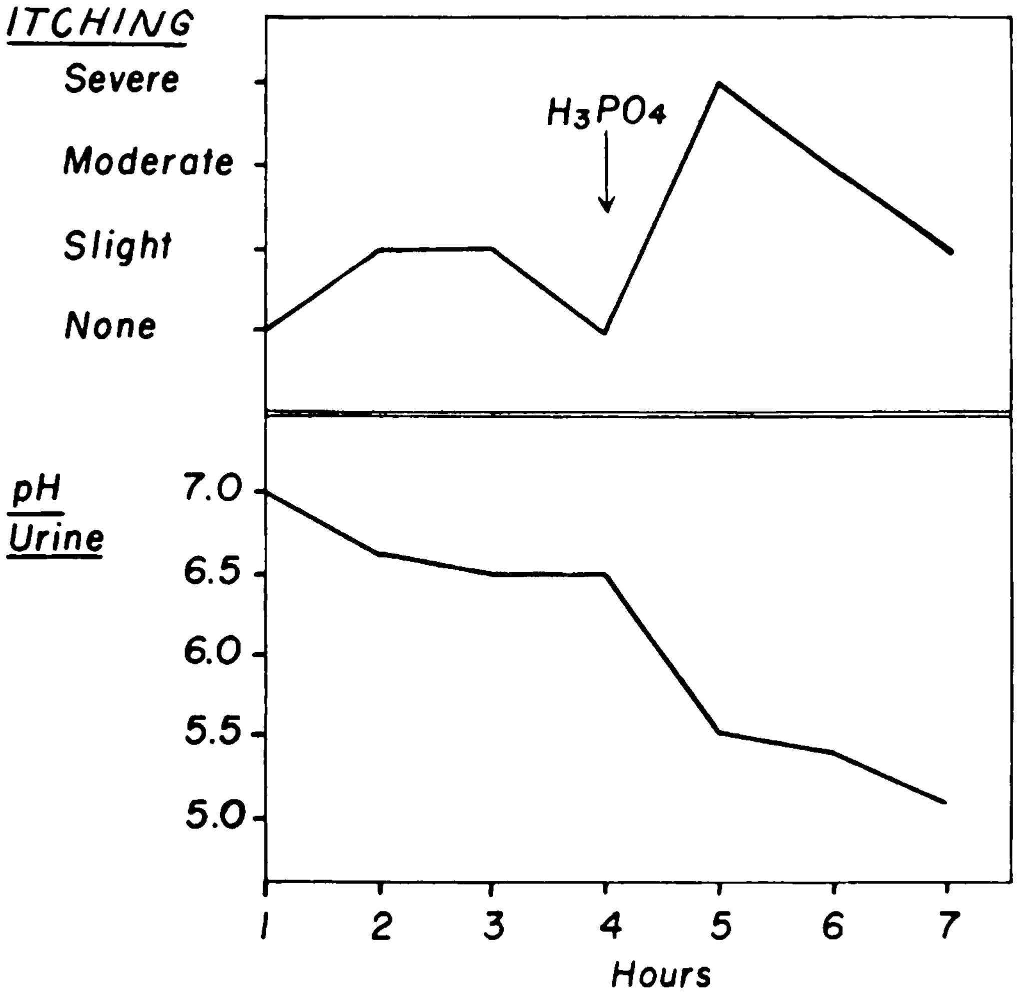

FIG. 22. Administration of phosphoric acid—1.5 cc phosphoric acid, sol. 50%—induces together with an acidification of the urine, an increase in the intensity of the *itching* with an *acid pattern*.

There is a distinct parallelism between the two curves in Figure 20, indicating that itching was more intense when the urine was relatively more alkaline, and slight or absent when the urine was more acid. We have considered this as an "alkaline pattern" of itching in accordance with the designation for pain. An inverse relationship between the two curves is seen in Figure 21. In this case, itching was more intense when the urine was more acid, and less severe when the urine was more alkaline. This represents an acid pattern.

The effect of a strong acidifying agent, phosphoric acid, in cases with acid and alkaline itching, is illustrated in Figures 22 and 23. The intensity of the alkaline itching in the first case was reduced by the acidifying action of phosphoric acid, while the acid itching of the second case was intensified. In Figure 24, the response of a patient with alkaline itching to the administration of sodium bicarbonate is shown. The intensity of itching was greatly increased after the alkalizing agent was given.

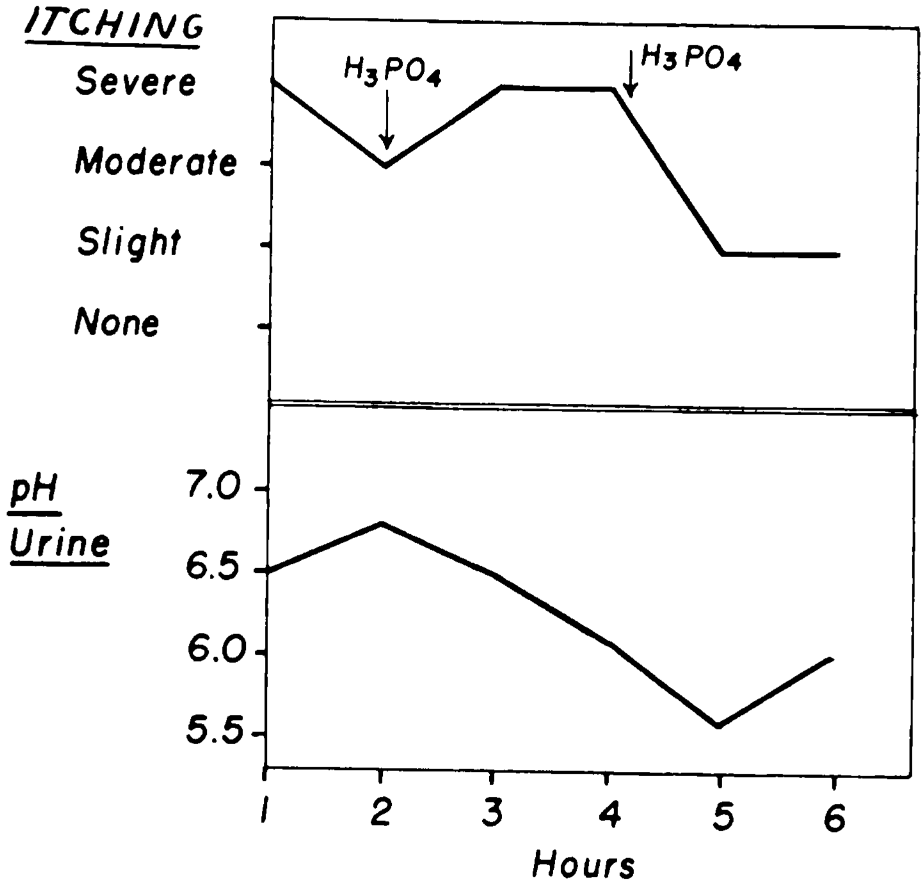

FIG. 23. Itching with an alkaline pattern is reduced in intensity by the administration of an acidifying agent. In the above example, two doses, each of 1.5 cc phosphoric acid (50%), were necessary in order to obtain this effect.

The fact that both pathological pain and pathological itching undergo the same changes in intensity related to the general acid-base balance would indicate that a similar mechanism may be involved in the pathogenesis of both symptoms. It can be conceived that a slight local pH change confined to the skin or mucous membrane could act on the itching end organs and evoke the sensation of itching. More intense pH would result in pain. The fact that itching, one of the principal symptoms of dermatological conditions, can be related to local acid and alkaline changes within the skin would permit the integration of skin pathology in a more general physiopathological mechanism. The concept of the intervention of two different

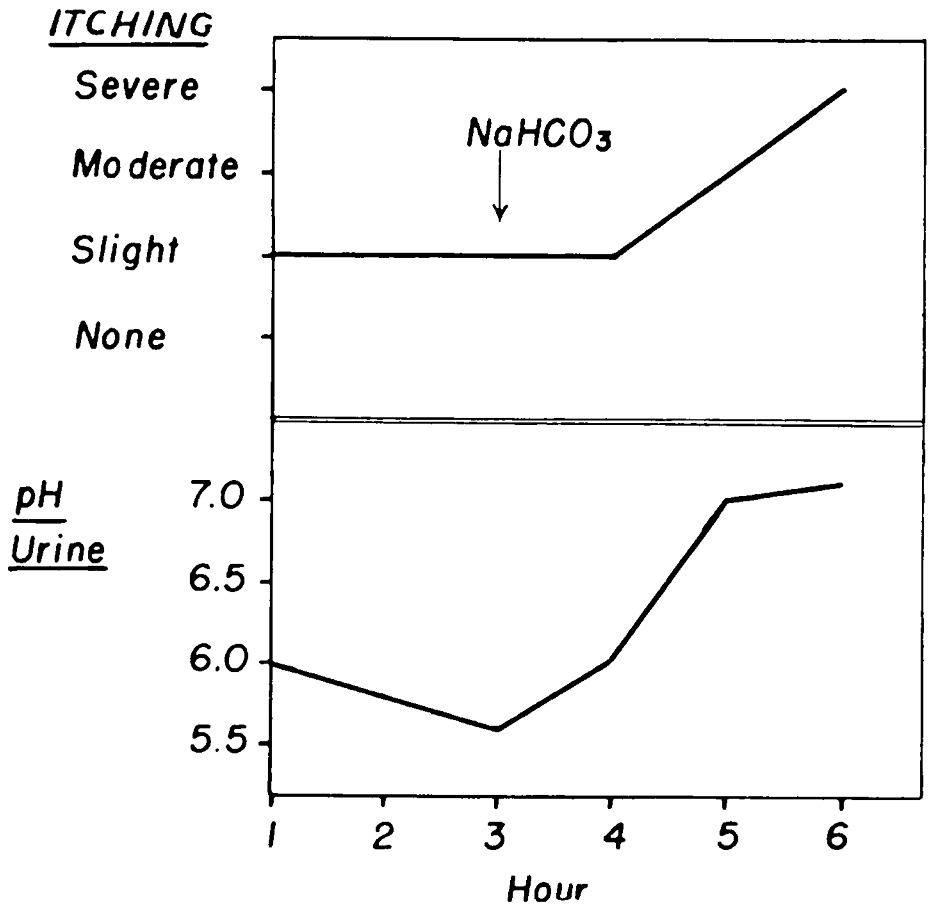

FIG. 24. The administration of 4 grams of sodium bicarbonate to a subject with an *alkaline pattern* of *itching* induces together with the alkalinization of the urine, exacerbation of the symptom.

abnormal processes, one resulting in acid substances and the other in alkaline compounds, represents a new approach to the study of many skin conditions. The therapeutic application of this concept has produced interesting results. (See Chapter XIV)

Vertigo

Vertigo has been of special interest in our research. While it can be induced by various etiological factors, a basic dualism in its pathogenesis is evident.

Many patients with vertigo have been found to experience wide variations in the intensity of the symptom. Some have exacerbations in the morning, others in the evening. This observation suggested a possible dual pattern and we investigated vertigo by the same method used for the study of pathological pain.

In patients with vertigo, the intensity was determined at hourly intervals by using either a scale ranging from 0 to 10, or a series of qualifica-

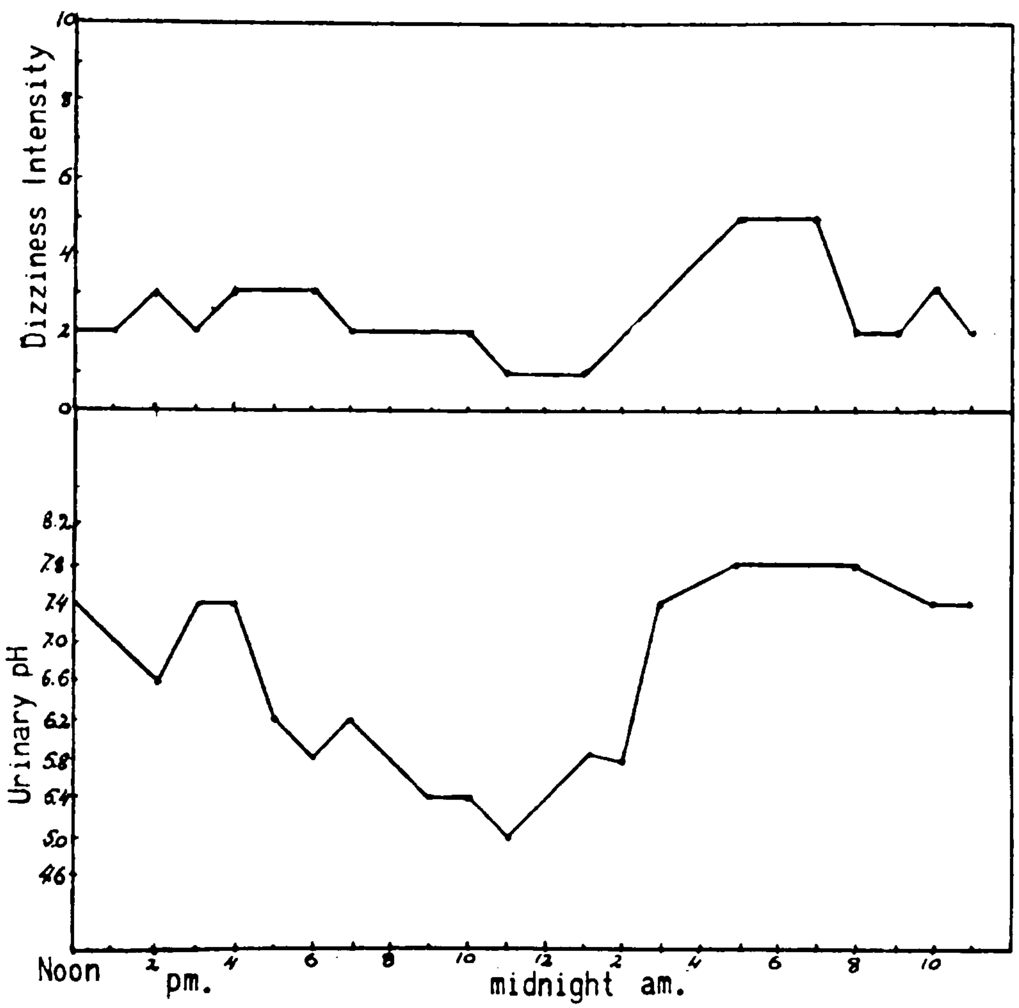

FIG. 25. Shows the curves of the intensity of *vertigo* and of the urinary pH in a case with an *alkaline pattern*, the variations of the two curves being parallel. (B. Welt, AMA Archives of Otolaryngology, *58*:273-300, 1953.)

tions, such as none, slight, moderate, severe, very severe and unbearable. At the same intervals, urine samples were collected and their pH values measured. Data were plotted in curves having time as common abscissa. Here again, as for pain, two different correlations could be observed. In some cases, the two curves—one for intensity of vertigo, and the other for urinary pH level—showed parallel variations. *(Fig. 25)* The vertigo became more intense when the pH was high, and this was considered to be vertigo

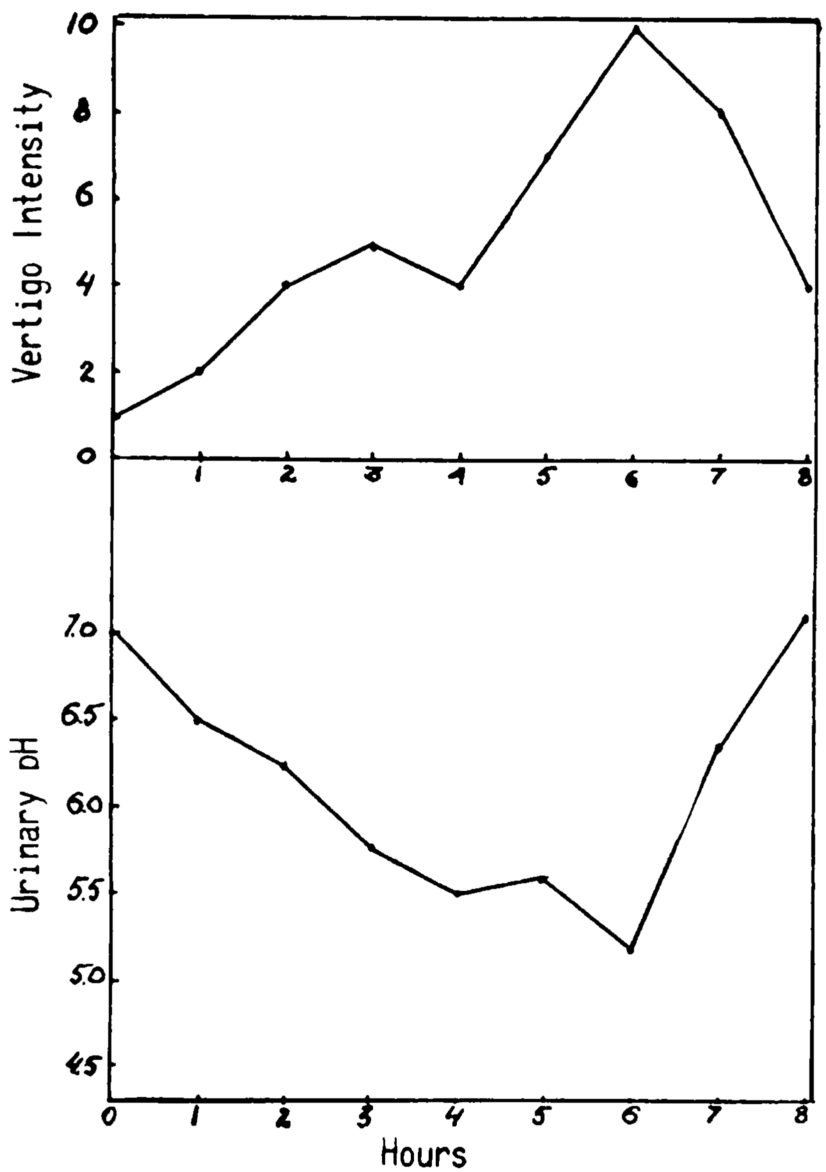

FIG. 26. *Vertigo* with an *acid pattern*. The symptom is more intensive when the urinary pH values are lower. (B. Welt AMA Archives of Otolaryngology, *58*:273-300, 1953.)

of an alkaline pattern. In other cases—of an acid pattern—vertigo was more intense with lower values of urinary pH. *(Fig. 26)*

The acid-base pathogenesis of vertigo was further confirmed by the response to acidifying and alkalizing agents. B. Welt has widely investigated vertigo by this method. He also has used the response to therapeutic agents as a criterion for the pattern present. The administration of butanol, heptanol or unsaturated fatty alcohols was seen to induce an increase in the intensity of vertigo of acid pattern and a decrease in the

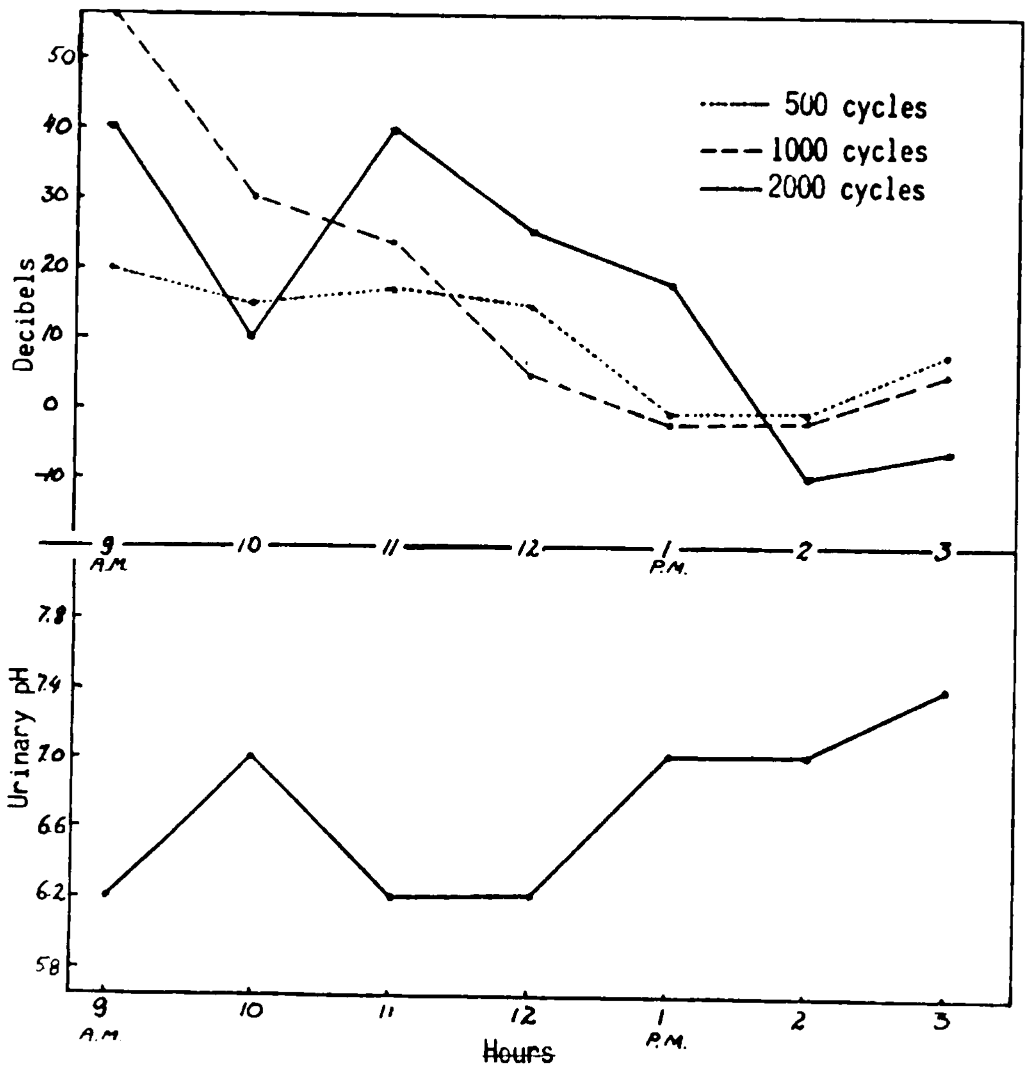

FIG. 27. The analysis of the concomitant changes in the curve of the intensity of the *auditive acuity* and of the urinary pH shows opposite variations in a subject with impaired hearing. The opposite variations are especially manifest for some values—2000 cycles in this case. This relationship corresponds to an *acid pattern*. (Courtesy of Dr. B. Welt.)

alkaline type. Agents such as sodium thiosulfate have an opposite effect.

The great similarity in the response of pain and vertigo to the same agents has established the role of acid-base changes in the pathogenesis of vertigo as well as the possibility of influencing these changes in order to relieve the symptom. These studies have shown that, in spite of the variety of etiological factors which can induce vertigo, the condition can be considered, from the point of view of therapy, in terms of its dualistic pathogenesis. This has simplified the therapeutic approach, limiting it to a choice between only two groups of agents. We will see later how successful this approach has been in Welt's hands.

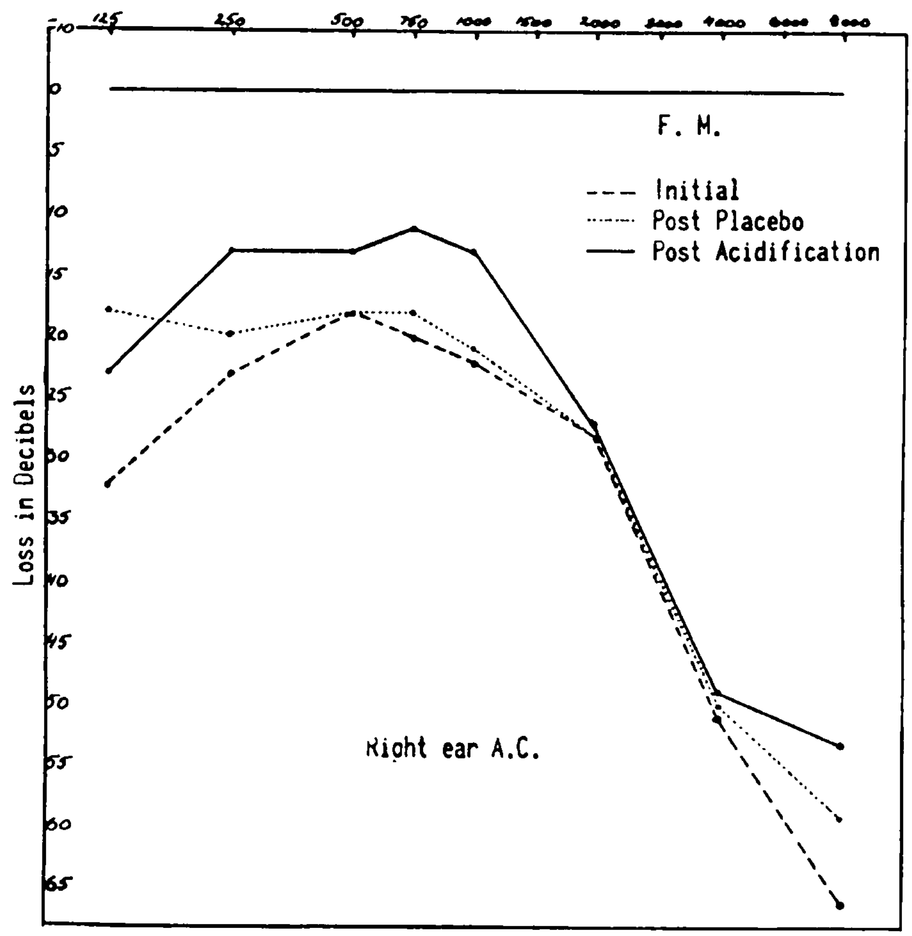

FIG. 28. The administration of an acidifying agent—2 grams of monoammonium phosphate—induces a marked increase of the *hearing acuity* if the abnormality present corresponds to an alkaline pattern. Only minimal or no changes are seen to occur if a few drops of acetic acid are used as placebo. (Courtesy of Dr. B. Welt.)

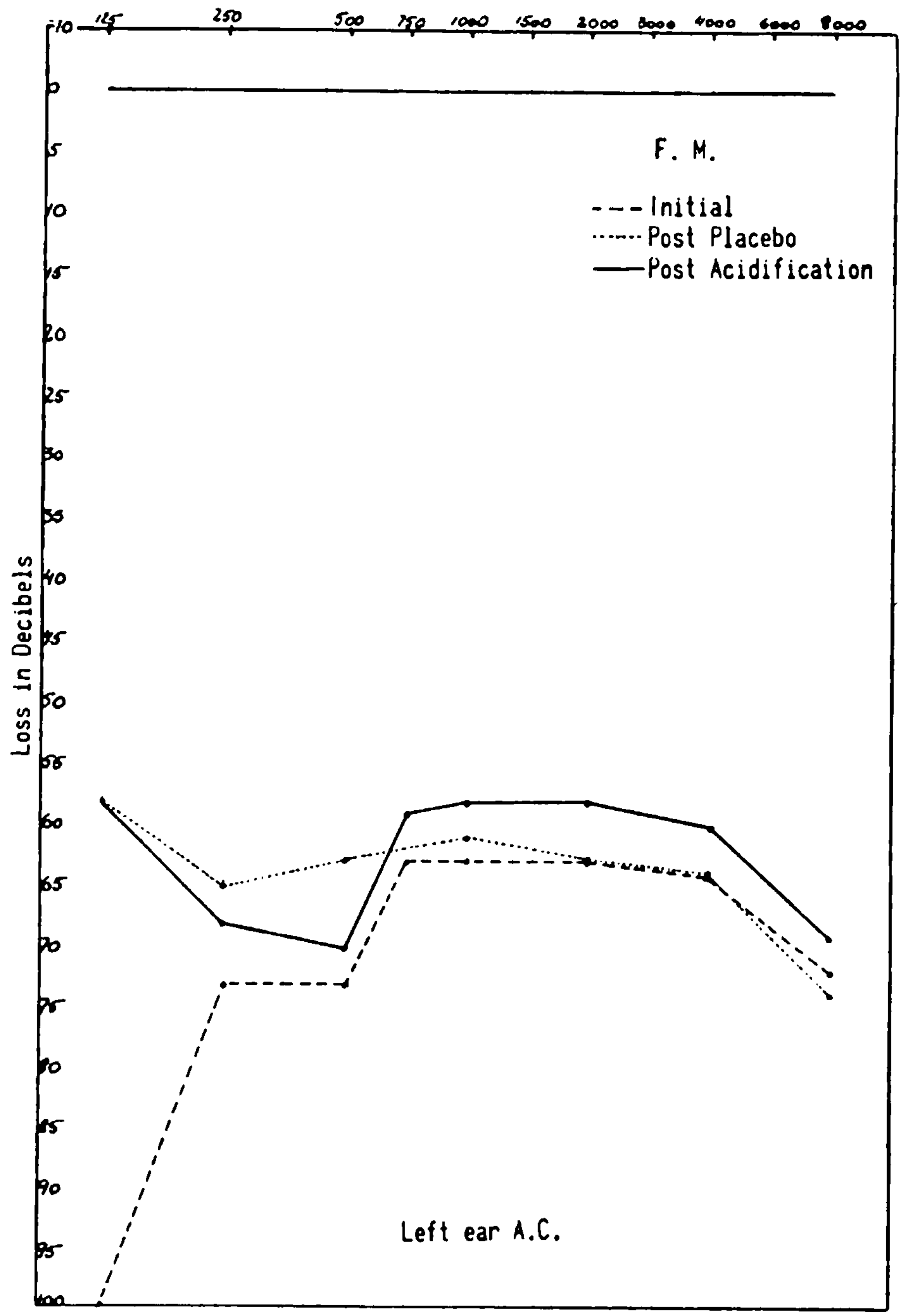

FIG. 29. Alkaline pattern of hearing impairment corresponds to an increased hearing acuity following the administration of 2 grams of ammonium phosphate.

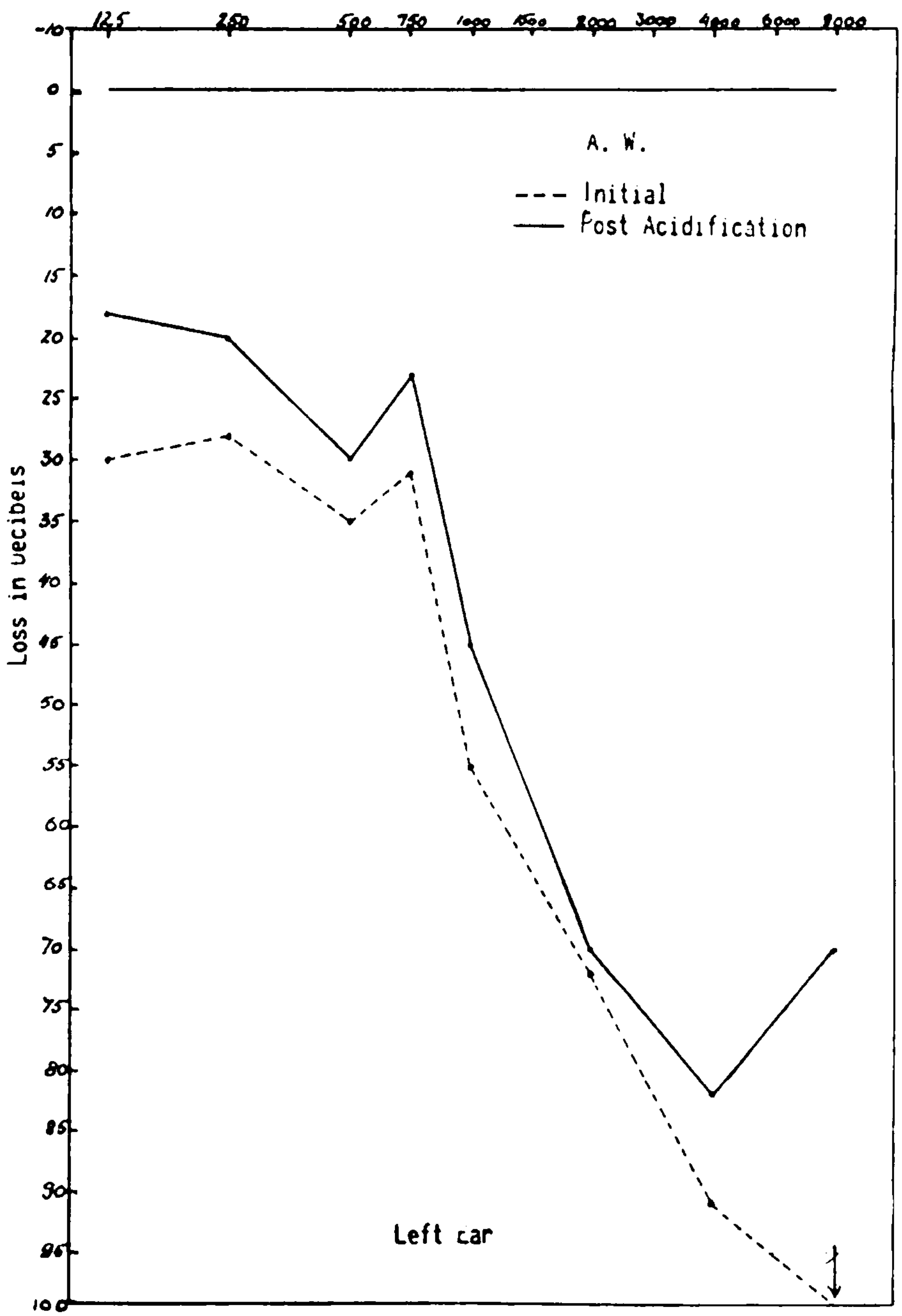

FIG. 30. Alkaline pattern of hearing impairment.

Impaired Hearing

In studying the various otological problems, B. Welt and I noted that many patients with impaired hearing experienced variations in auditive acuity at different times of the day, or even in conjunction with food intake. This led us to investigate impaired hearing by the same method used for pain. *(Fig. 27)* We studied the influence of acidifying and alkalizing agents upon auditive acuity in cases of impaired hearing.

Complete audiograms were obtained, employing differences of only two decibels between measurements and using all of the accepted frequencies for air and bone conduction. Audiograms were obtained in subjects before and after administration of acidifying agents, such as ammonium

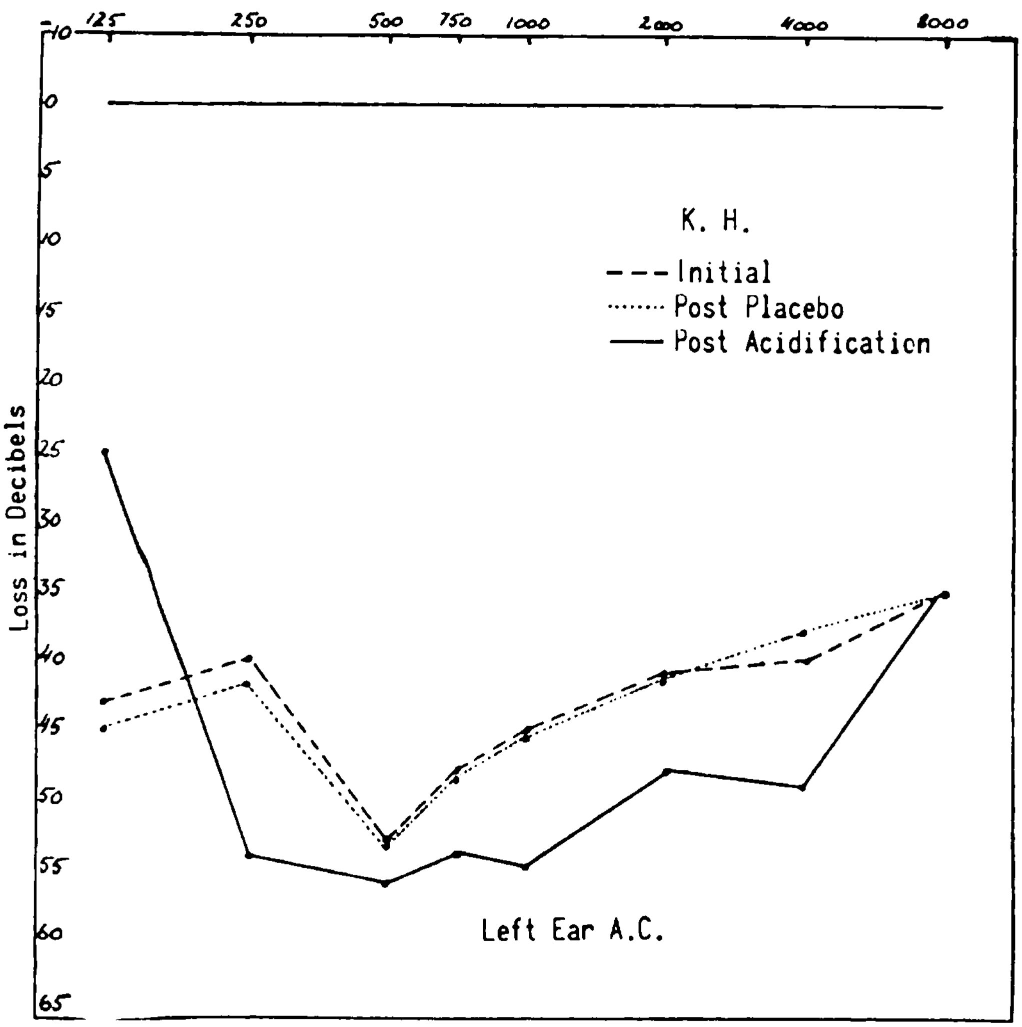

FIG. 31. The administration of 2 grams of monoammonium phosphate induces a decrease in hearing acuity if the abnormal pattern is acid.

chloride and ammonium monophosphate, and alkalizing agents such as sodium bicarbonate. In normal subjects, the audiograms showed little or no change. In subjects with impaired hearing, three types of responses were noted for any one agent. The audiogram was either not changed at all or an increase or decrease in acuity was seen. If a manifest increase in acuity

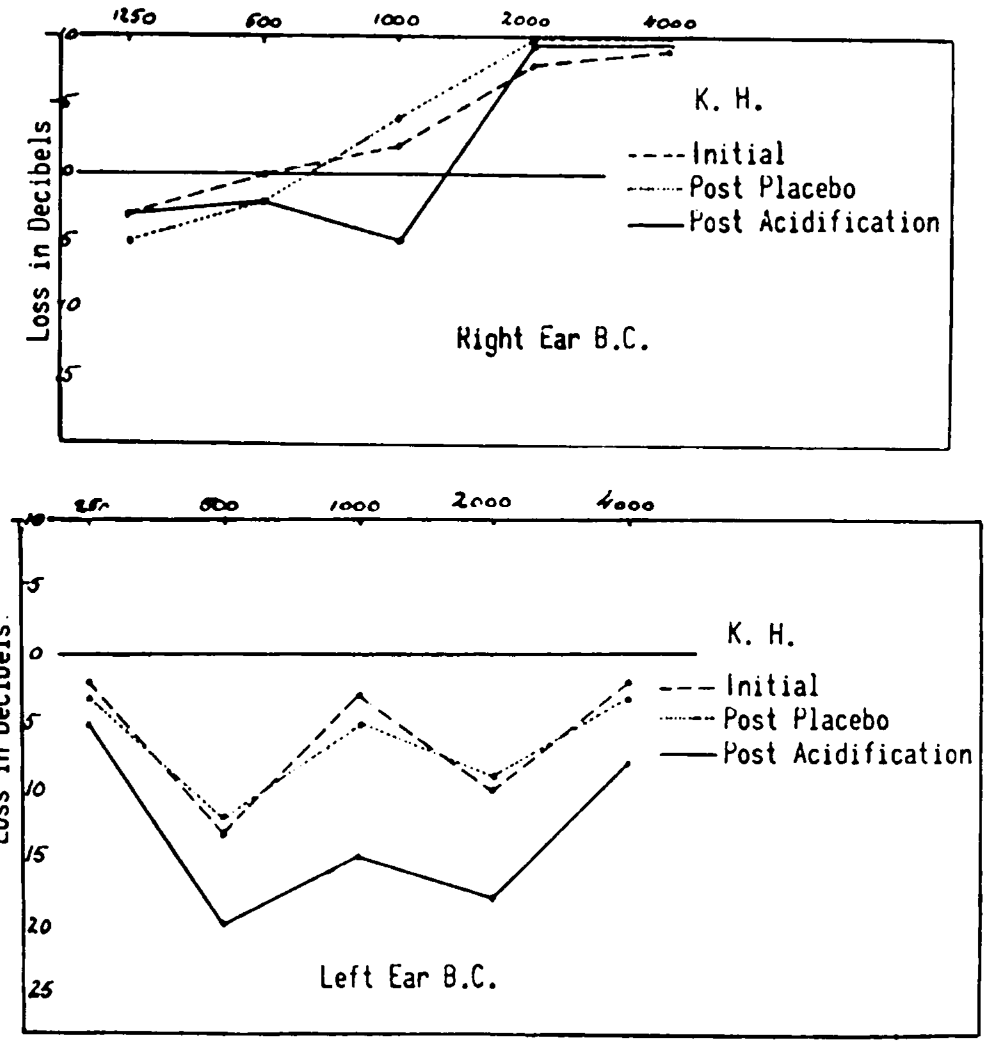

FIG. 32. Acid pattern of hearing impairment.

was obtained with one group of agents, an opposite effect was obtained when an agent of the opposite group was administered.

Changes of at least 6 decibels were required before they were considered to be induced by an agent. When changes of such intensity were obtained with an agent, it was invariably true that opposite changes would be obtained with an opposite agent. It was also true that the same responses could be obtained in the same patient in repeated tests. This appears to be highly significant, indicating that the response was, in fact, correlated with changes induced by the administered agent, changes similar to those seen in the case of acid-base symptoms. It was thus possible to integrate hearing impairment in the group of acid-base symptoms and to recognize two well-defined types, one corresponding to an acid pattern, the other to an alkaline. Figures 28 through 32 illustrate several cases taken from Welt's observation. It must be noted that changes under the influence of the agents are seen at almost all frequencies in some cases but at only certain frequencies in others.

It must be noted also that not all cases of impaired hearing could be placed in one or the other category. While this could be done almost without exception for young subjects or for those with still evolving conditions, it could not be done for subjects with old, fully evoluted impairment. It appears that once the pathological processes have arrived at a terminal point—and an inactive sclerotic scar is present—a response to acidifying or alkalizing agents is no longer to be expected.

Manic-depressive Condition

We have studied the relationship between intensity of manifestations and systemic acid-base balance of the body in another group of subjects with various mental disorders. Of all the cases studied, the only condition in which a clear relationship could be shown was in manic-depressive subjects. From patients presenting changes during the day, passing from periods of high excitation to calm, from deep depression to calm, we obtained hourly urine specimens. At the same time, observations of their mental state were made. The evaluations of mental condition were made by trained observers or members of the family using a conventional scale which permitted translation into graph. The pH of the urine samples was measured electrometrically. Curves of the pH and of the mental conditions were plotted having the common time as abscissa. A striking correlation between the two curves was found in the first investigations in manic patients. With the pH of the urine at higher values, the patient was calm, while the more acid urine corresponded to periods of intensive agitation. Figure 33 shows an example.

This correlation also could be demonstrated by administering acidifying and alkalizing substances to manic patients. Acidification through the administration of phosphoric acid was followed by a manifest increase in agitation while administration of an alkalizing agent—sodium bicarbonate

—was followed by a period of calm. An opposite but less evident correlation was seen for several depressed patients. We must mention that the usual difficulty of judging accurately the degree of depression from one hour to another can explain this lesser correlation. Manic manifestations were much more readily evaluated.

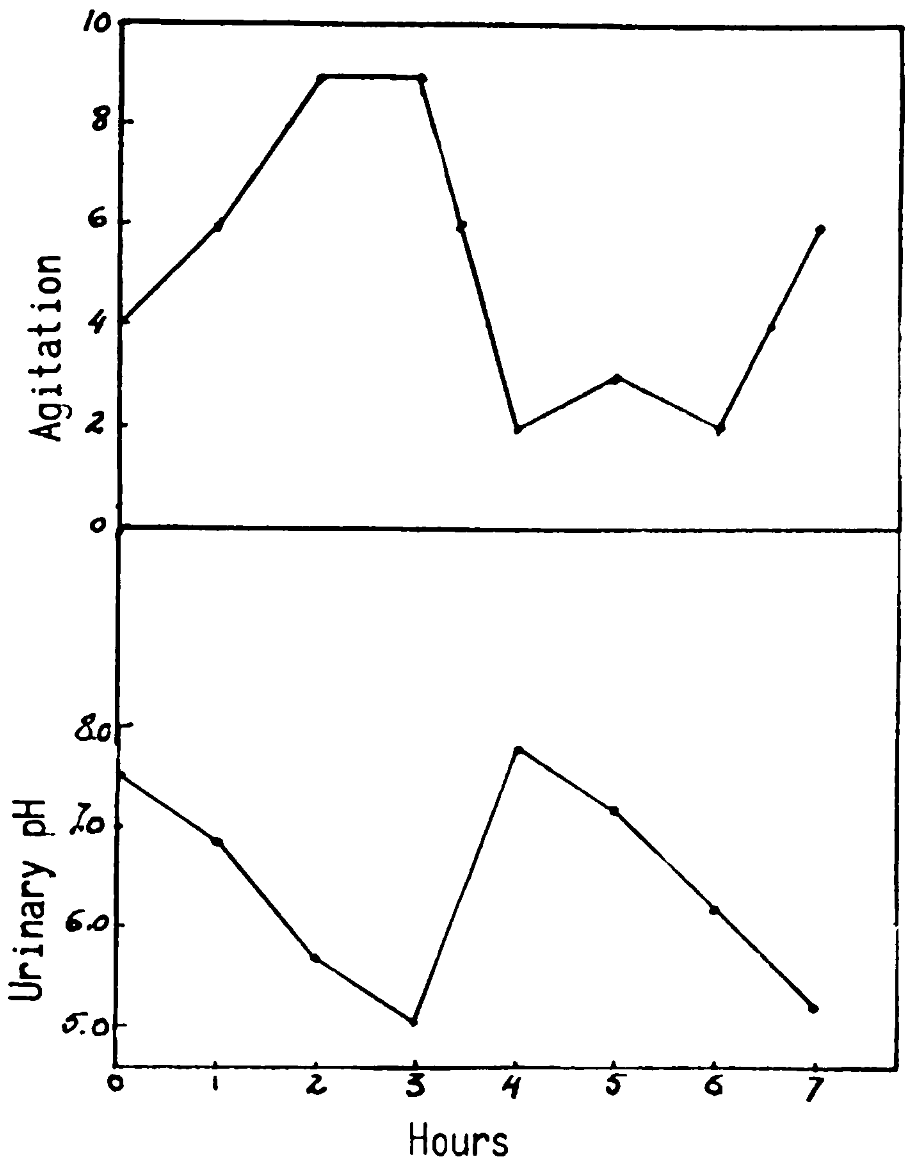

FIG. 33. The variations of the curve of the *agitation* of a 10-year-old boy are opposite to that of the urinary pH, indicating an *acid pattern*.

Dyspnea

Certain characteristics of dyspnea suggested that this symptom might be explored by the same means employed in studying pain associated with pathological tissue changes. A regular pattern is observed in certain types of dyspnea related to the time of day. Cardiac asthma or paroxysmal cardiac dyspnea occur mainly at night after patients have gone to sleep. However, this is not due to the recumbent position since patients may assume this position during the day without any ill effect. Harrison's "evening dyspnea" (20) is characteristically absent in the morning, but develops slowly during the course of the day, reaching a maximum in the evening.

Just as for pain, the degree of intensity of dyspnea was studied in relation to hourly acid-base balance changes as indicated by changes in the pH of the urine. Patients having dyspnea of prolonged duration as a result of various pathological conditions, with no treatment of any kind for at least six hours before or during the period of observation, were the subjects of this investigation. The degree of intensity of the dyspnea was estimated by trained observers who were in constant attendance. Dyspnea was recorded by the observers as absent, slight, moderate, severe, or very severe, estimations being based upon rate depth and evident difficulty in respiration.

At the time of these observations, hourly urine specimens were obtained from patients with as little disturbance as possible. No patient showed evidence of renal disease. The pH of the urine specimen was determined potentiometrically. The curves showing hourly fluctuations in the intensity of the dyspnea and the changes in the pH of the hourly urine specimens were then plotted and compared. Acidifying and alkalizing substances were administered to patients during the course of some tests in order to observe the influence of induced changes in the acid-base balance upon the degree of dyspnea. Phosphoric acid and sodium bicarbonate were used for this purpose.

Fourteen patients with different pathological conditions were studied. In ten cases, a distinct correlation between the intensity of the symptom and acid-base variations was found.

Four patients had pulmonary edema associated with the symptom of dyspnea. One patient had edema due to congestive heart failure; another had pulmonary edema and lung metastases from a carcinoma of the pancreas. Two other patients with cancer of the breast metastatic to the bone and skin also had pulmonary edema. In one of these, the pulmonary edema appeared to be a result of the accidental introduction of a fatty acid in oil preparation into the blood stream following an intramuscular injection. In all four of the cases with pulmonary edema, the intensity of dyspnea was found to be increased when the urinary pH showed changes toward more alkaline values and was diminished when the pH changes were opposite. In these cases, the intensity of the dyspnea was relieved following admin-

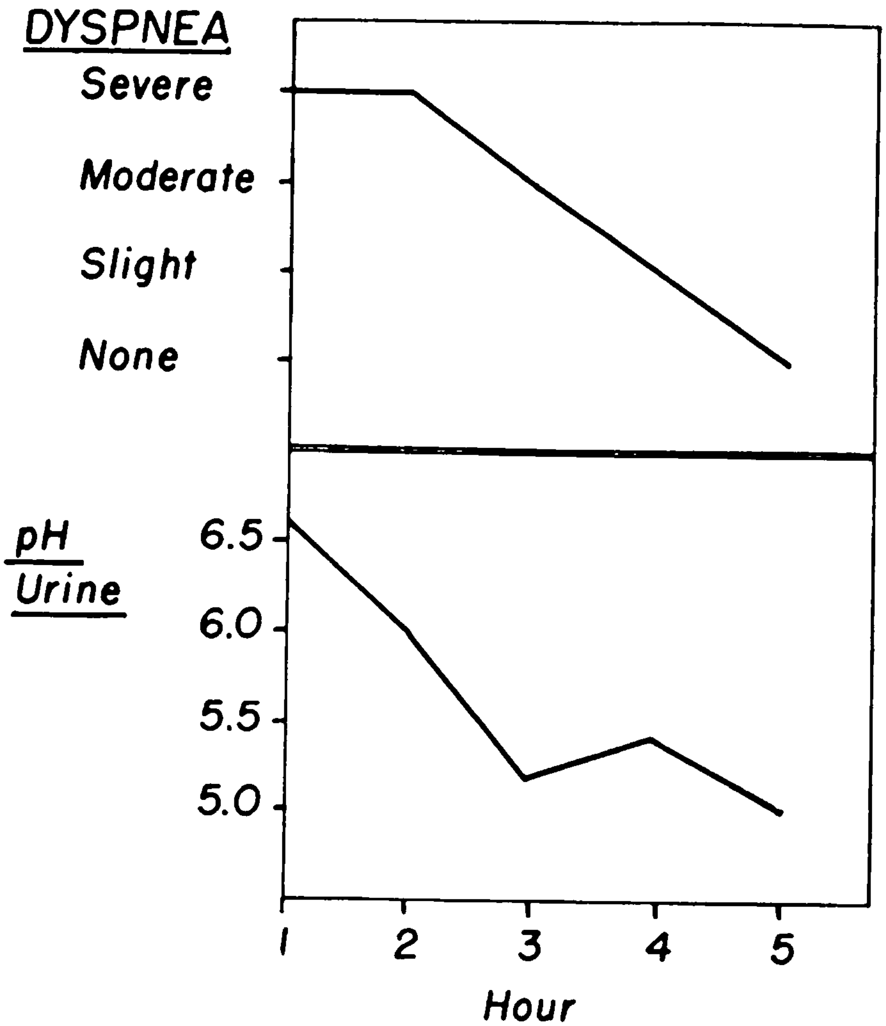

FIG. 34. The parallel variations between the curves of the intensity of *dyspnea* and of the value of the urinary pH in a case of pulmonary congestion following an accidental intravenous injection of a fatty acid preparation, indicates an *alkaline pattern*.

istration of phosphoric acid, while sodium bicarbonate increased the dyspnea. By analogy with pain, we called this correlation an alkaline pattern. *(Fig. 34)*

Six cases showed an opposite type of correlation between the intensity of dyspnea and the acid-base changes in the pH of the urine. All of these cases had mediastinal or pulmonary masses and failed to show signs of pulmonary edema. In these cases, the maximum degree of dyspnea was associated with a relatively more acid urine, and the dyspnea was less intense when the urine was more alkaline. In these cases, phosphoric acid increased the degree of dyspnea, while conversely sodium bicarbonate decreased it. This would correspond to an acid pattern of dyspnea. *(Figs. 35, 36)*

These findings, although obtained in only a limited number of patients, strongly suggest a similarity between the fundamental origin of both pain and dyspnea. As in pain, the two patterns of dyspnea were associated with a relative alkalosis and a relative acidosis.

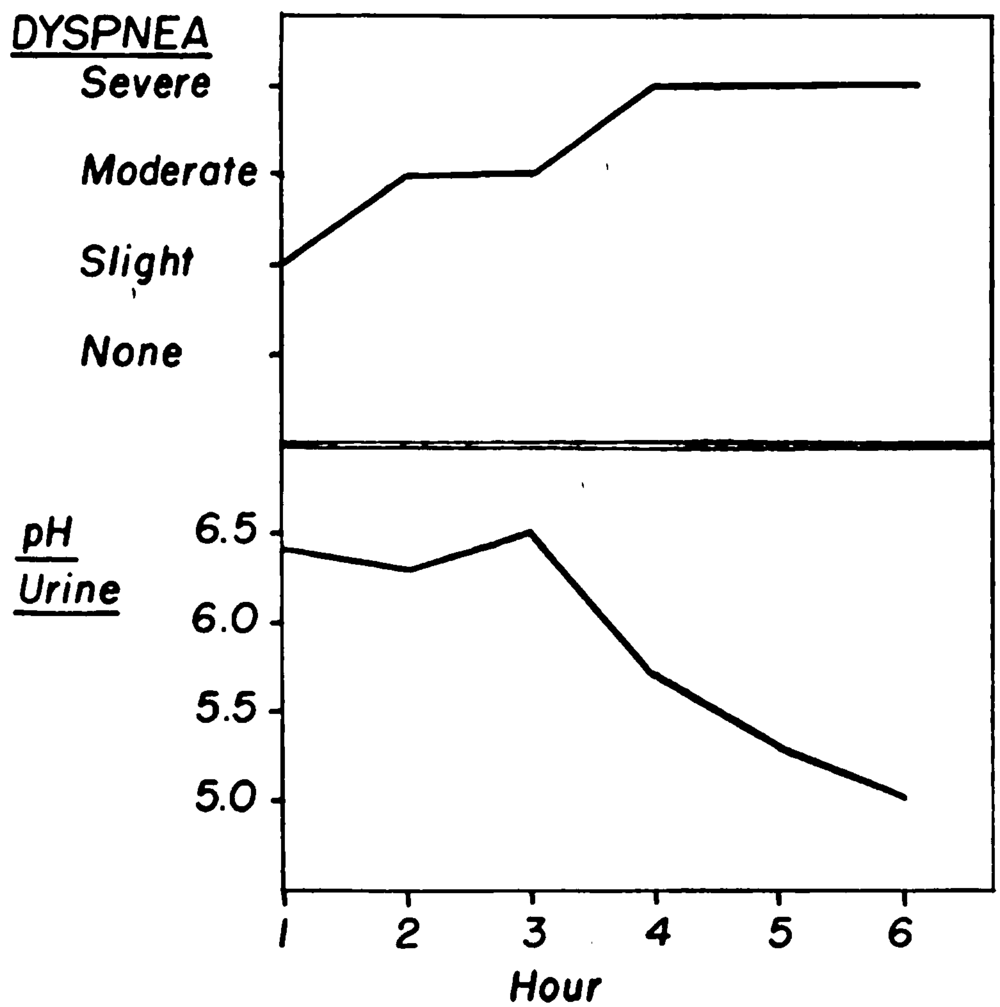

FIG. 35. The opposite concomitant variations between the intensity of *dyspnea* and urinary pH in a case of mediastinal metastases of a hypernephroma indicate an *acid pattern*.

Certain differences exist between the investigations of pain and dyspnea. In studying pain, it was necessary to depend entirely upon the observations of the patient as to the relative intensity of the pain experienced from hour to hour. In dyspnea, the patient's own observations were found

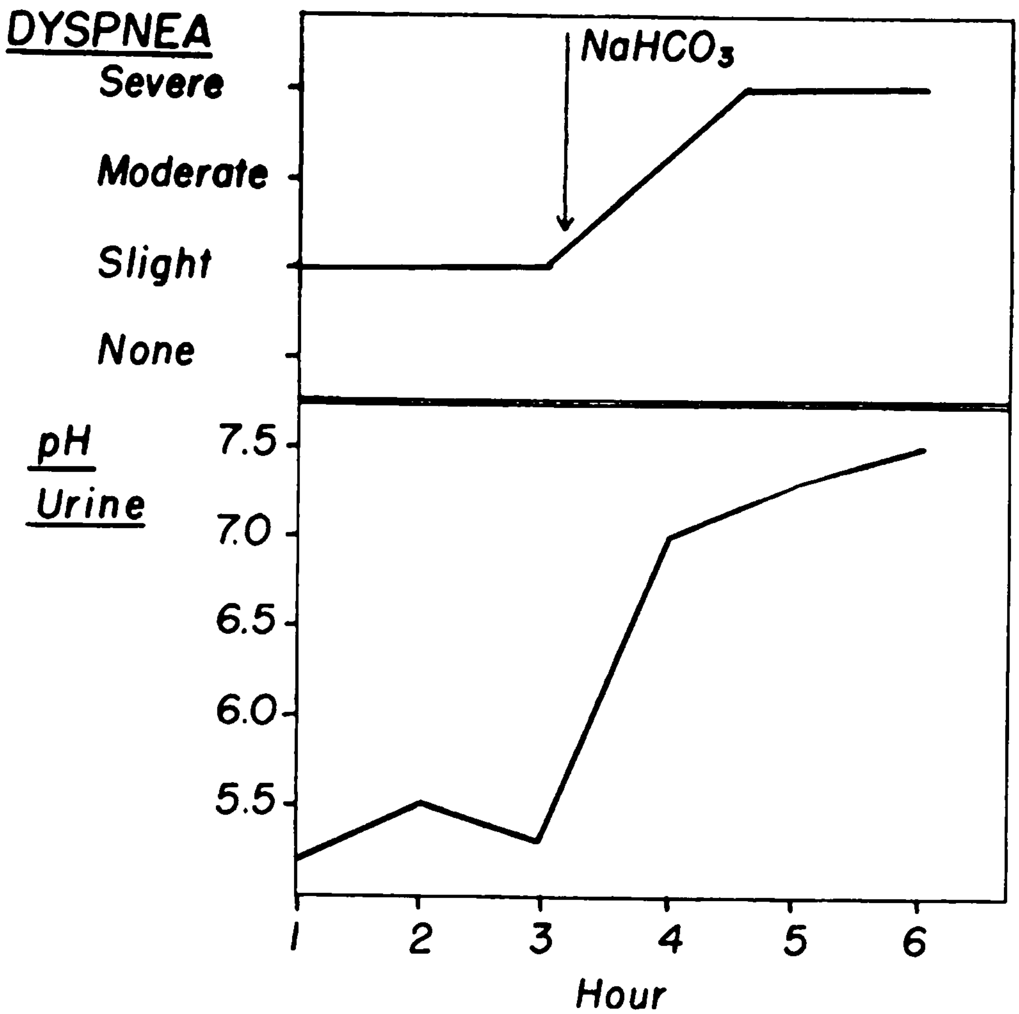

FIG. 36. The administration of sodium bicarbonate increases the intensity of the *dyspnea* in a case of pulmonary metastases of cancer of the gall-bladder, indicating an alkaline pattern.

to be less reliable due to the emotional factors associated with dyspnea. It was, however, possible to depend upon trained observers who could estimate accurately enough the degree of dyspnea on the basis of rate, depth and apparent difficulty of respiration. It was found that the greater the experience of the observer, the closer was the correlation between the curves of intensity of dyspnea and the changes of the urinary pH values.

Since it appeared evident that acid-base changes play a significant role in influencing the degree of dyspnea experienced by the patient in two opposite directions, it was important to consider this influence in relation to the physiology of respiration which is known not only to be affected by, but even dependent on acid-base changes.

Concerning the respiratory center, two different mechanisms of direct chemical stimulation have been suggested as being responsible for dyspnea. One is lack of oxygen, but considerable evidence exists to indicate that simple anoxemia is not a true cause of dyspnea. (21, 22) On the other hand, an acidosis of the respiratory center is known to cause dyspnea, but it has been established that only a very profound general acidosis, such as that connected with diabetes, acid poisoning or emphysema can create a change in blood pH sufficient to affect the respiratory center. This is also true for the chemoreceptor centers located in the carotid sinus, which are still less sensitive to the general lack of oxygen or acidosis than the respiratory center. While general acid-base changes seem to play an important role in dyspnea, these chemical changes would not appear to act directly upon the respiratory center since the actual blood pH is not sufficiently changed.

Other factors—involving direct local, rather than systemic influences—may be considered. One such direct action would be related to reflex stimulation which is generally accepted as having an important role in the control of respiration and even dyspnea. This reflex control of respiration is connected with nerve endings within the lung parenchyma which are stimulated when the walls of the alveoli are stretched in the respiratory phase. The stretch reflex induces impulses, carried by way of the vagus, which acting upon the respiratory center, stop the inspiratory phase and bring about expiration. It may be assumed that the nerve endings within the parenchyma can be stimulated not only by mechanical changes within the parenchyma but also by local chemical changes too. Under abnormal conditions such as pulmonary congestion, there may be a change in the tissue reaction, as has been recognized by a higher pH of the edema fluid itself. Through this reflex mechanism, these pulmonary tissue reaction changes may produce dyspnea. The general acid-base fluctuations influencing the local alkalosis would, as seen in pain, indirectly influence the degree of dyspnea. Such a mechanism may account for dyspnea with an alkaline pattern found in pulmonary congestion.

A similar local factor also could be seen for the acid pattern. It was observed that all patients with an acid pattern of dyspnea had tumors located within the mediastinum or in the lung parenchyma itself. From the study of pain, we know that abnormal degrees of acidosis can occur in tumors. pH changes toward acidosis within a tumor tissue in the vicinity of chemoreceptors may produce impulse discharges in these centers especially sensitive to changes toward acidosis. They may alter the character of respiration and result in dyspnea. As in other conditions, these local changes occur even with reduced changes in the systemic acid-base balance. Through this mechanism, variations in the intensity of dyspnea can occur without the intensive change in the general acid-base balance which is considered necessary to affect directly the respiratory center itself.

The fact that relatively small acid-base balance changes affect the intensity of dyspnea in two opposite directions can thus be explained by this indirect influence exerted upon a local process, leading to alkalosis in abnormal conditions affecting the pulmonary parenchyma and to acidosis in lesions present in the neighborhood of the chemoreceptive centers. These two mechanisms proposed as part of this working hypothesis, appear able to explain the paradoxical experimental findings in clinical studies of this symptom, where opposite responses upon dyspnea are seen for the same acidifying and alkalizing agents.

A more complete study of dyspnea under this aspect will be published separately.

Dualistic Patterns at Other Levels

Cellular Level

Cytological studies have revealed that some characteristics of the cell, other than those typifying the cancerous anomaly itself, exhibit dual patterns. For the cellular level, they could ultimately be related to changes in the aging processes. In tumoral foci having an acid pain pattern, cytological characteristics indicate a prolonged cellular youth. A round aspect of the nucleus, with a fine texture of chromatin and well-separated nucleolus, and a basophyl cytoplasm represent major characteristics of cellular youth. In lesions with an alkaline pain pattern, the cells show rapid early aging. The tendency to lobulation of the nucleus, to separation of chromatin and formation of clumps, to cytoplasmatic oxyphily and the appearance of azurophyl granulae characterize such aging. Rapid aging was seen to lead to premature cellular death through piknosis and karyorrhexis. Opposite cellular aging processes could be further related to differences seen in evolution of tumors. Rapid aging of cells, associated with alkaline pain patterns, results in necrotic tumors and ulceration of superficial lesions. Frequently, it could be noted that a change from acid pattern to alkaline occurs and is accompanied by a melting away of massive tumors and their replacement usually by ulceration.

Tissular Level

As seen above, pain, dyspnea, vertigo and itching can be considered tissue level manifestations which show dualism. Additionally, the nasal pH *(Note 5)* deviates either toward acid or alkaline values and these deviations can be correlated with similar acid-base changes at the tissular level. These measurements are useful as a diagnostic criterion for tissue level changes.

Organic Level

The same dualism observed at the cellular and tissue levels also was found in signs and symptoms involving the organ level. Dual patterns were found for dysfunctions of various organs. Insomnia and somnolence, diarrhea and constipation, oliguria and polyuria, tachycardia and bradycardia, all represent examples of dualism at the organic level.

The dualism evident for the length of persistence of a wheal *(Note 6)* induced by intracutaneous injection of a saline solution was also related to the organ level with the skin considered to be an organ. In normal subjects, the resorption of the wheal is completed in about 15-20 minutes. In one group the resorption time is short, even reduced to a few minutes. In other groups, on the contrary, the resorption time is greatly prolonged, the wheal sometimes being present even after more than 90 minutes.

Systemic Level

Studies of dualism at this level covered temperature variations and changes in various blood and urine values.

Temperature

Two patterns of temperature changes were found in cancer patients. For oral temperature, 37°C (98.6°F) was considered as the reference value. Temperatures measured several times during the day showed that, for many patients, the values were fixed either above or below this reference line. Normal individuals exhibit daily variations of temperature; the curve not only crosses the reference line but also shows broad changes. In contrast, variations usually are smaller in abnormal cases, and the curve remains on one or the other side of the reference line. Figures 37, 38 and 39 show examples of such curves. The two patterns have been found to be

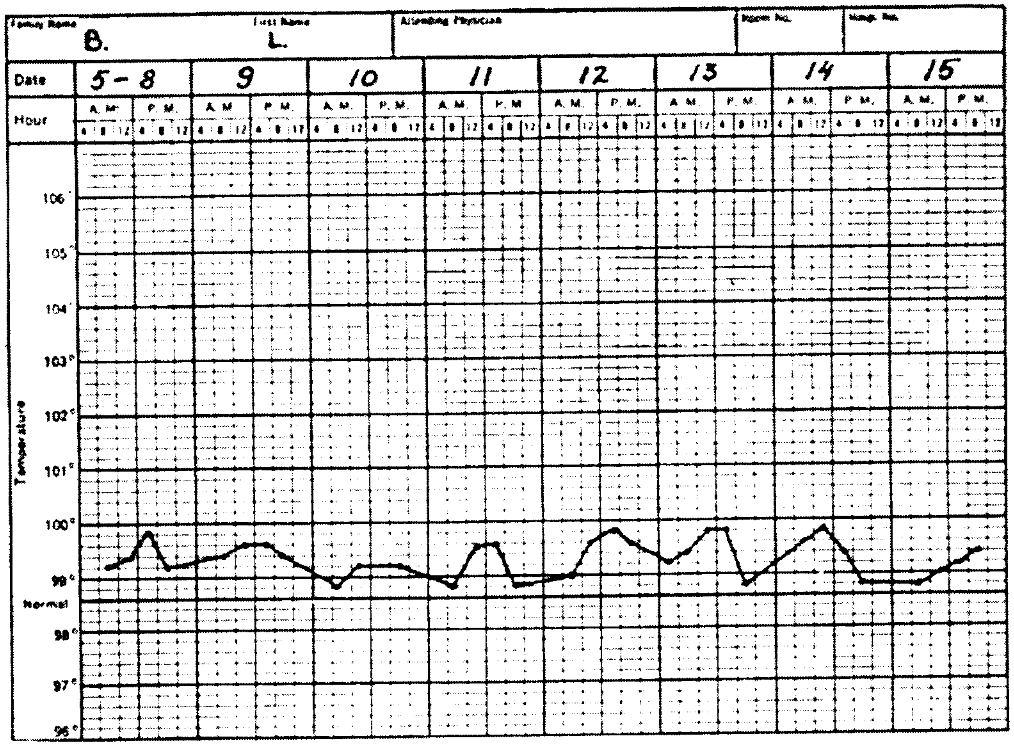

FIG. 37. The curve of oral *temperature* of a case with generalized metastatic melanoma is persistently *above* the 98.6°F (37°C) line, which corresponds to the average value of normal individuals.

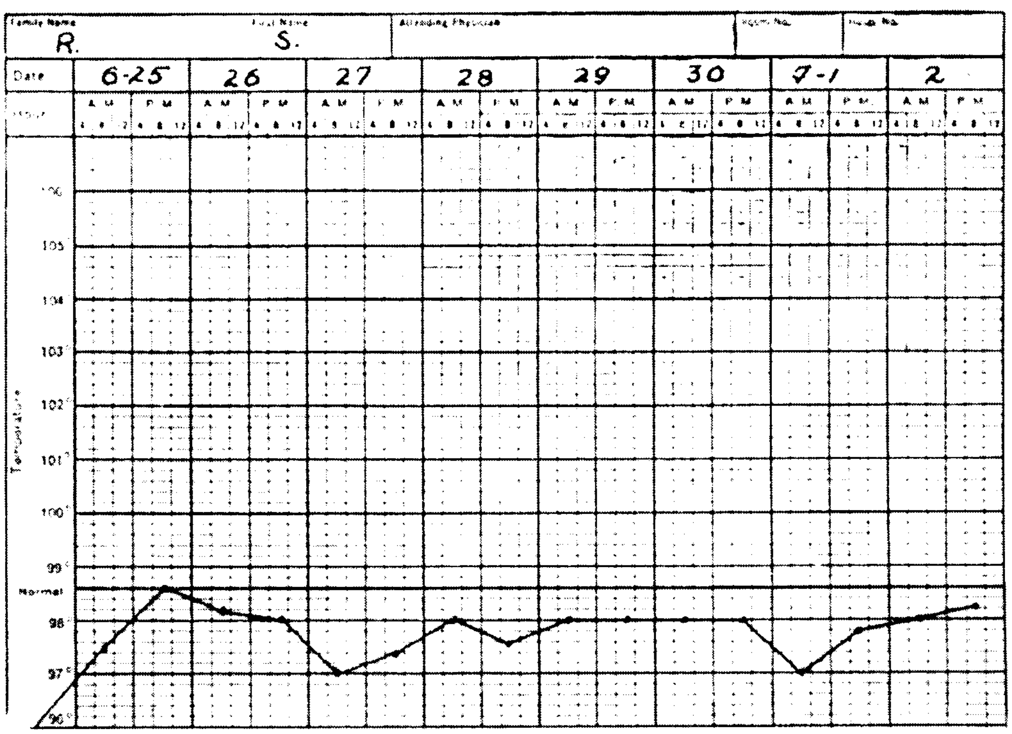

FIG. 38. The curve of the oral temperature of a patient with generalized metastases of adenocarcinoma of the breast shows values constantly *below* the 98.6°F average line.

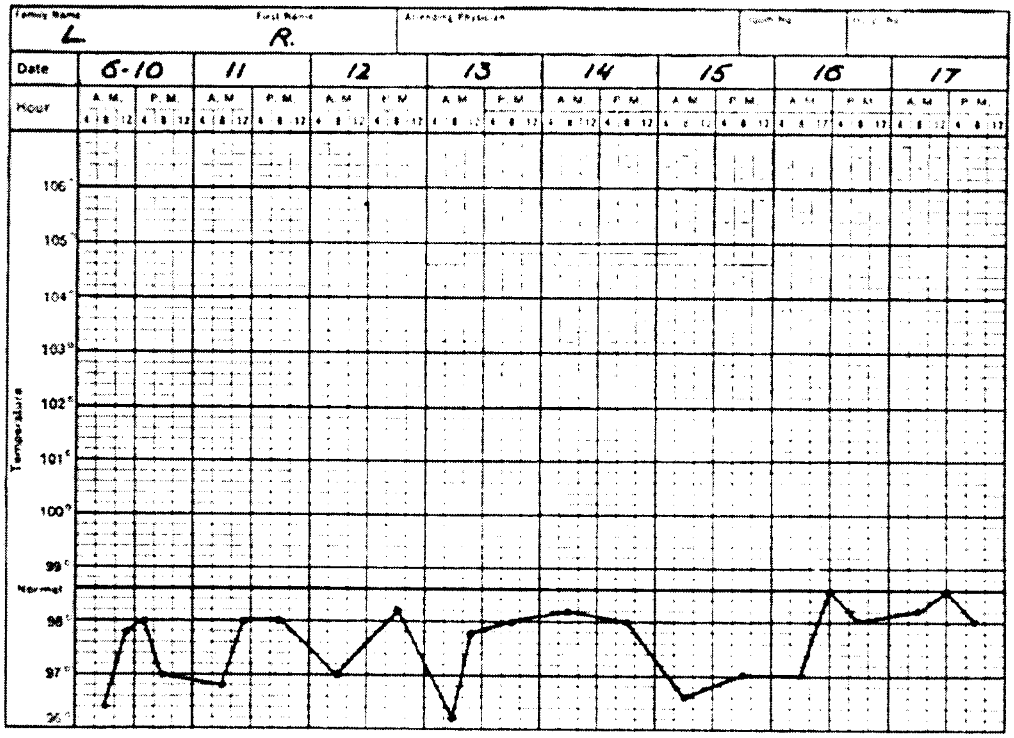

FIG. 39. Curve of the oral temperature of a patient with bronchogenic cancer with abdominal metastases shows values constantly *below* 98.6°F (37°C) average line.

independent of type or site of origin of tumors. We will discuss the significance of temperature patterns later.

Systemic Analyses:

Changes in urine or blood values were followed in hundreds of subjects for long periods, even years. It appeared essential to plot the data graphically. An average value, obtained from a significant number of normal subjects, was represented in graphs as a reference line. In normal subjects, as a general rule, relatively wide oscillations occur around the average value line. By contrast, in disease states, there is a fixation of the curve on one or the other side of the average value, the curves exhibiting only slight, or even no, variations. Two opposing patterns are thus evident in disease states for each type of analysis of blood and urine. The dualism indicates once again the existence in systemic metabolism of two kinds of abnormal changes with antagonistic characteristics. It is important to note that the advanced cancerous condition is characterized by a marked dualistic pattern at the systemic level.

Blood

In blood analyses, the concentrations of potassium and calcium, the presence of C reactive proteins, the number of leucocytes and of circulating eosinophiles, *(Note 7)* and the red cell sedimentation rate, have been studied, using classical methods. They all show the same dualism. Figs. 40 to 43 show some of these curves with the average values as reference lines. With the intention of obtaining information concerning the amount of potassium present in cells, we investigated the content of this cation of the red cells. *(Note 8)*

Urine

In urine studies, measurements were made for pH, specific gravity, surface tension, oxido-reduction potential, excretion of sodium, potassium, calcium, chlorides, phosphates, sulfates, sulfhydryl, indoxyl, glucuronic acid, peroxides, etc. Most studies were carried out by routine test techniques. For some analyses, however, conventional techniques were found to be inadequate and new tests devised.

For the urinary excretion of sulfhydryl, a new technique was devised by M. Bier and P. Teitelbaum in our laboratories. Using the Warburg micromanometer, the nitrogen liberated from sodium azide in a buffered solution in the presence of free iodine was found to be directly related to the amount of sulfhydryl present. The amount of nitrogen freed at a determined moment—13 minutes—was most indicative. *(Note 9)*

For the information which we needed concerning the amount of calcium in urine a very simple method was devised. *(Note 10)*

For measurement of urinary surface tension, we devised a new technique. We used a capillary so calibrated as to give the surface tension in dyne/cm for a fluid with a specific gravity of 1.015. In this method, several arrests or slowdowns of the descending column are noted and make it possible to obtain information about an extremely important factor which is usually not considered in the measurement of surface tension with other methods. It is known that urine is formed of different constituents, some of them with the tendency to move toward the surface while others tend to move toward the bulk of the fluid. Changes in the distribution of these constituents take place. They induce changes in the value of the surface tension of the urine which occur even during the time measurements are taken. The descending column in a capillary will indicate these changes which are important for precise measurement of surface tension of urine. *(Note 11)*

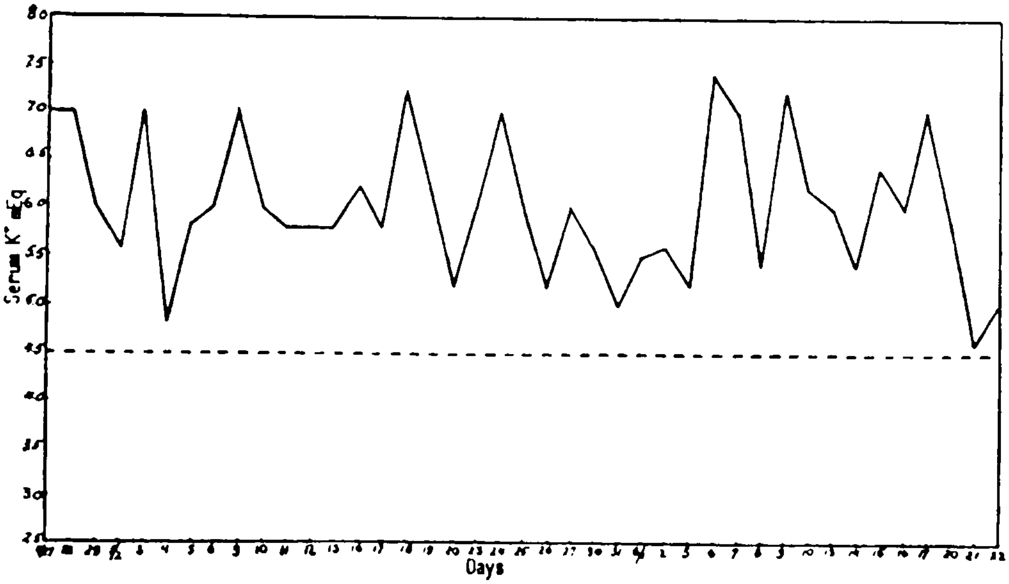

FIG. 40. Curve of the value of the K^+ *in blood serum* in a case with periarteritis nodosa. The values remain *above* 4.5 mEq, which represent the average value obtained from series of normals.

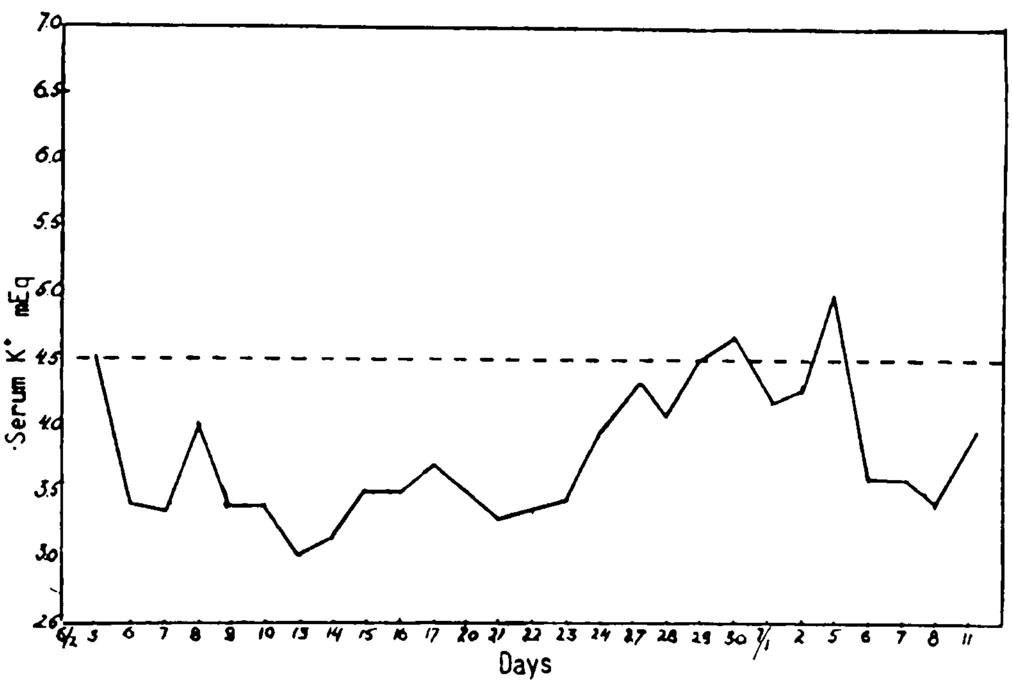

FIG. 41. Curve of the values of K^+ in the blood serum of a subject with carcinoma of the breast, liver metastases and jaundice. The values remain almost constantly below the 4.5 mEq line.

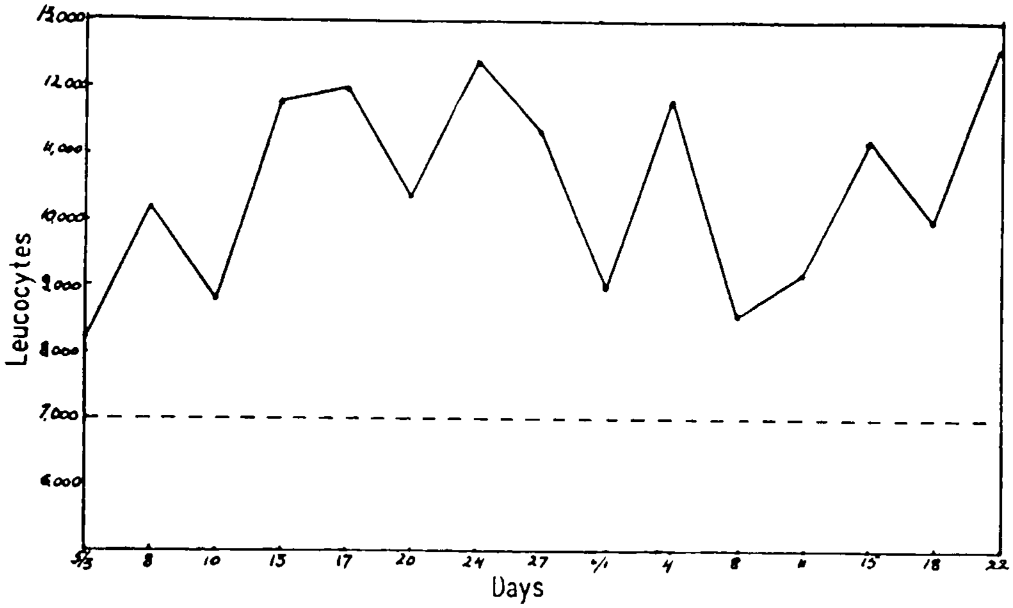

FIG. 42. The curve of the number of blood leucocytes of a case of breast adenocarcinoma shows constantly values above 7.000, considered as the average value for normals.

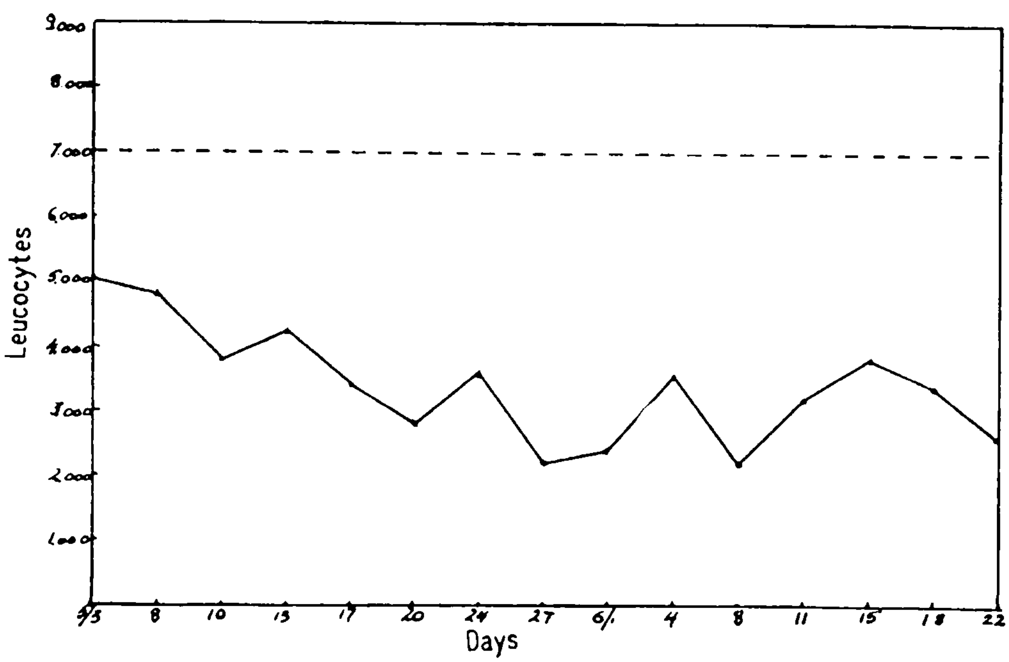

FIG. 43. The curve of the number of blood leucocytes of a case of breast carcinoma shows persistently values below the average line of 7.000.

Two methods were employed to measure the oxido-reduction potential of urine. In one, the measurement was made with a potentiometer using a platinum electrode, first at the pH of the urine and once again after bringing the pH to 7 by adding the necessary amount of NaOH or HCl. *(Note 12)* In the second technique, differences in potential were measured through the time necessary to discolor a solution of toluidine blue in an acid medium at 100°C. The value was determined in seconds, the concentration of the dye having been chosen so that discoloration in 100 seconds represented an average value for normal subjects. More rapid discoloration indicated higher potential, while a low potential corresponded to slow or even no discoloration. *(Note 13)*

The presence and relative amounts of oxydizing substances in the urine were also investigated by means of two reactions: in one, through the passage of indoxyl into indigotine and indigorubine under the influence of sulfuric acid *(Note 14)*; in the other, through liberation of iodine from iodides in the acid medium.

It is interesting to mention at this moment, the variations encountered in the metabolism of nitrogen and the form under which it is excreted through the kidney under normal and pathological conditions. We could show that in general the form of excretion is determined by the amount of water also excreted by the organism. High amounts of water will thus induce the excretion of nitrogen principally as ammonia, low amounts as uric acid. This relationship was explained by data found in comparative physiology. The availability of water in the environment of various animals was seen to determine the form under which these animals excrete nitrogen. The occurrence of similar conditions concerning the excretion of water in pathological states, furnishes an interesting explanation for the form under which it is excreted in these pathological conditions. In Note 15 this problem is discussed in more details.

In all tests requiring quantitative measurements, an important problem arose. It appeared practically impossible to obtain 24 hour urines routinely for periods of months in large groups of individuals in order to note the continuous changes in excretion of the different substances studied. Measurements of various substances eliminated in urine could be made under these circumstances only by using isolated samples. The values so obtained express the concentrations of the substances in the sample and consequently were directly related not only to the amount eliminated by the kidney but also to the amount of water excreted at the same time. The values varied greatly from one specimen to the next, according to the amount of water excreted. Therefore these data could only be of relative usefulness. Since specific gravity is also a direct function of the amount of water excreted in a urine sample, we related the concentration of a substance to the specific gravity of the same sample. This ratio provided a new value which is independent of the amount of water in the sample and is more closely related to the amount of the other substances which vary much less in amount than water. From the physiopathological point of view, the data obtained were seen to correspond to the degree of active reabsorption of a given substance by the kidney. While the ratio of the concentration over specific gravity would vary directly with the excretion of the substance, the inverse ratio would represent an index of retention, which increases with the retention of the substance in the body. Such indices were routinely applied for the different substances tested in urine to obtain more reliable values than could be obtained from the concentration data alone. *(Note 15)*

Urinary Patterns

Various urinalyses were performed during sufficient lengths of time on a larger number of subjects considered to be normal. For each test, an average value was thus obtained. This average value served as a reference line for the curves traced with the data obtained from the subjects. The

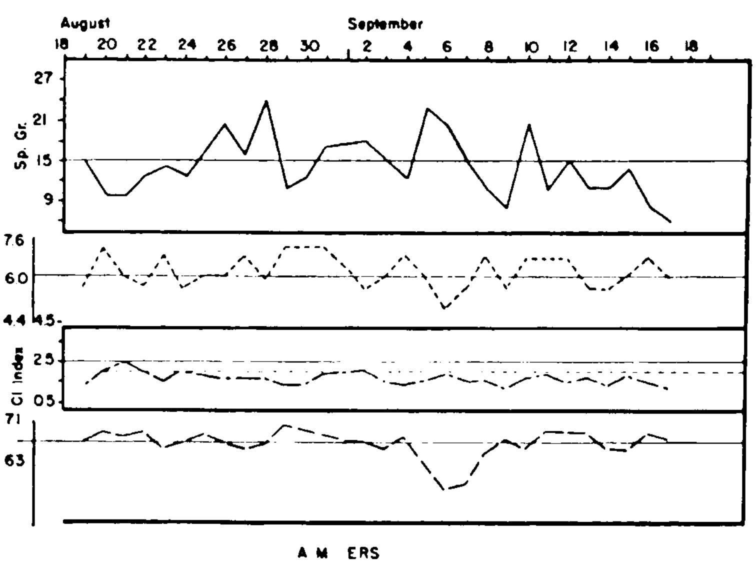

FIG. 44. Curves of *different analyses* of daily urine samples of a *normal* 40-year-old male. For each kind of analysis, the corresponding average value was calculated from the measurements obtained in more than one hundred normal subjects. The curves are seen to pass from one to the other side of the lines corresponding to the respective average values. A certain correspondence is seen for the changes which take place at the same time in these curves. Parallel variations are seen between specific gravity and chloride index, while opposite to those for the pH and surface tension.

study of these curves has permitted us to recognize several characteristic patterns. Under conditions considered normal, the curves were seen to pass from one side to the other on this average line with relatively wide variations. When an abnormality existed, the various urine analyses were characterized by a curve with only small variations, fixed on one or the other side of the average line. For each test, two such characteristic *abnormal patterns* are encountered. Fig. 44 shows the curves of different tests passing

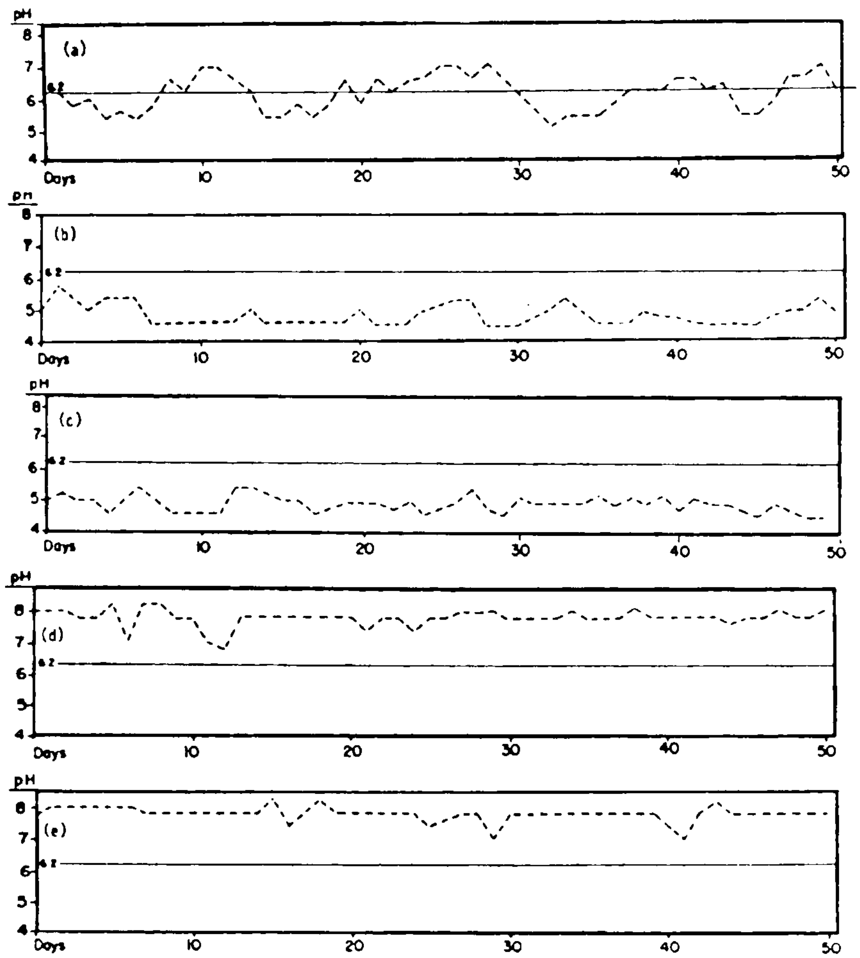

FIG. 45. Curves of the values of the *urinary pH* followed during 50 days in five subjects. The curve (a) corresponds to a normal individual while the other four (b, c, d, e) to subjects with different cancerous lesions. For the normal case, the values pass above and below the 6.2 value which is considered as the average computed values obtained from normals. For the abnormal cases, the curves which show little variations are fixed at one or the other side of the average line. For case (b), an adenocarcinoma of the ovary, and case (c), a bronchogenic cancer, the curves are fixed below the average line. For case (d), with a bronchogenic cancer, and case (e), a cancer of the breast with generalized metastases, the curves are above this average line.

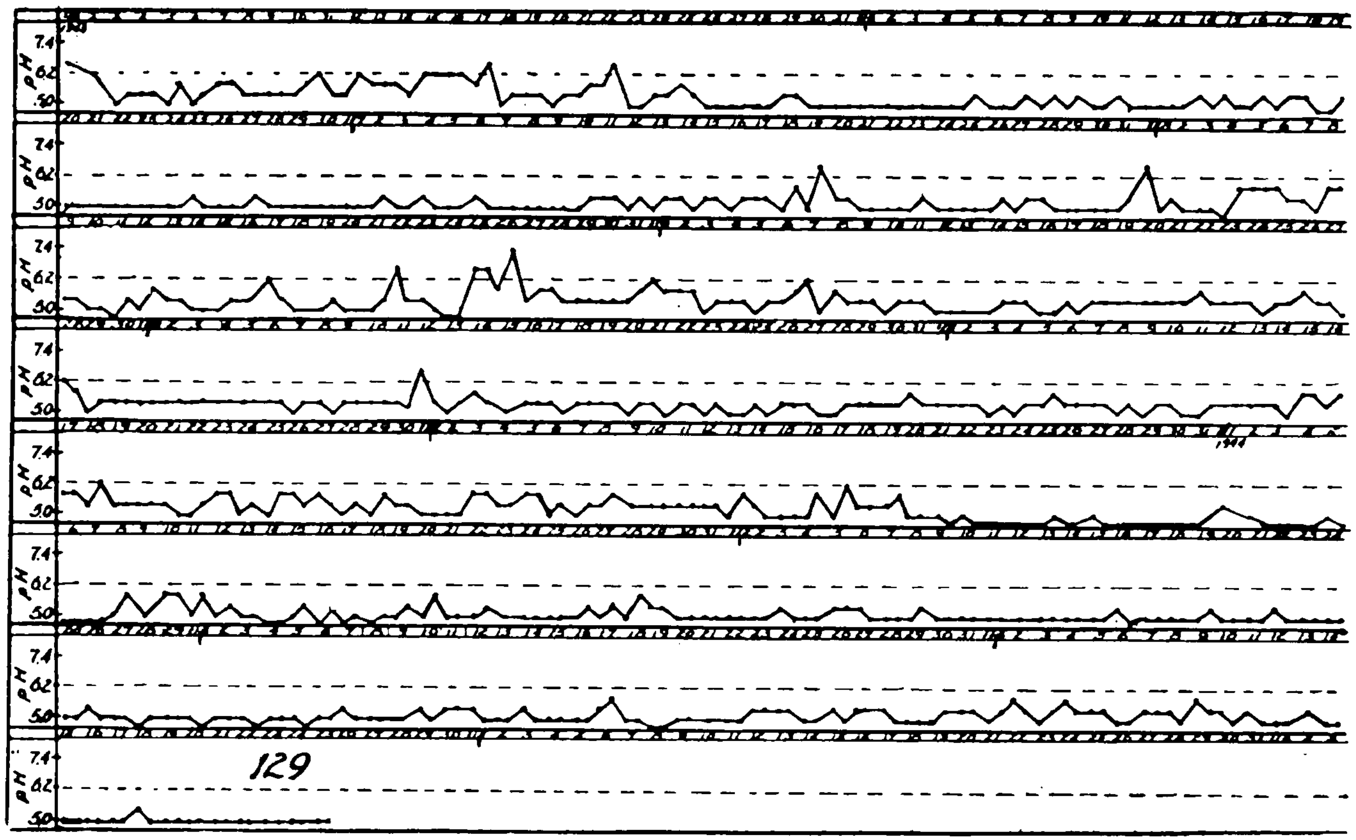

FIG. 46. *Urinary pH values* of a patient with a cancer of the prostate and multiple bone metastases measured in two daily urine samples for a period of more than 1½ years, remain fixed below the average value—6.2—independent of the changes in diet and of various therapeutic attempts. With the progression of the disease, the fixation of the pH at low values becomes more apparent.

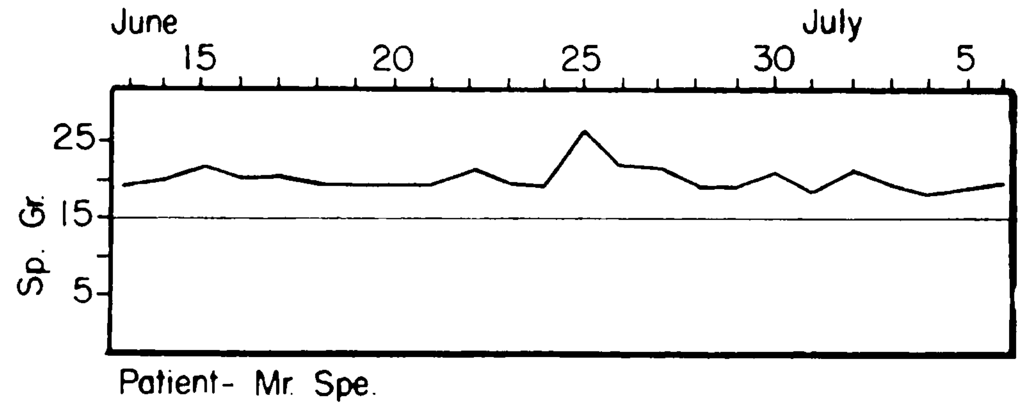

FIG. 47. Curve of the values of the urinary specific gravity in a case of cancer of the breast, with the values fixed above 1016 which is considered as an average value for the specific gravity as computed from a series of measurements in normals.

from one side to the other of the respective average lines as corresponding to a normal subject. Figures 45 to 51 show several examples of two opposite patterns for the various tests used such as urinary pH, specific gravity, surface tension, chloride index and sulfhydryl index.

Fundamental Offbalances

When the curves of various analyses obtained at the same time for the same subject were checked, an interesting relationship was found.

In patients with small localized tumors, only some of the analyses showed abnormal patterns. However, with the evolution of cancer toward the terminal stage, abnormal patterns became apparent for more and more analyses. In advanced cases, most of the analyses showed abnormal patterns.

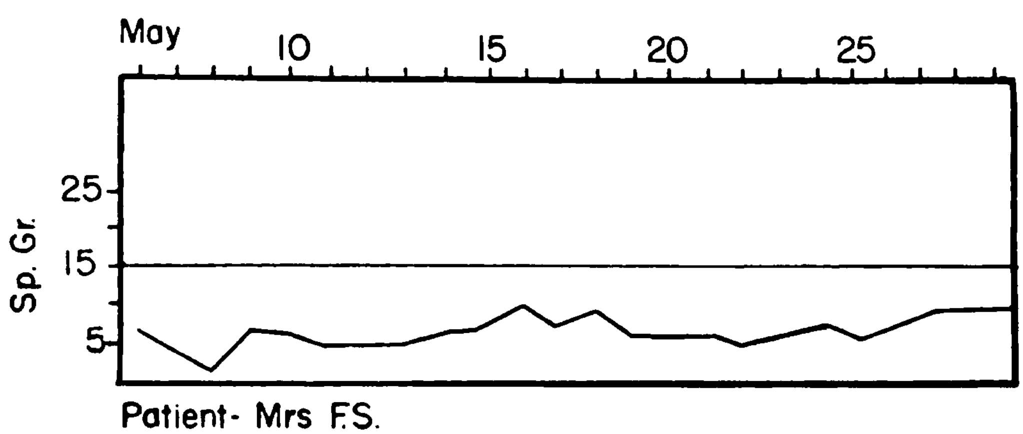

FIG. 48. The values of the urinary specific gravity in a case of cancer of the breast, are the whole time below the average value of 1016.

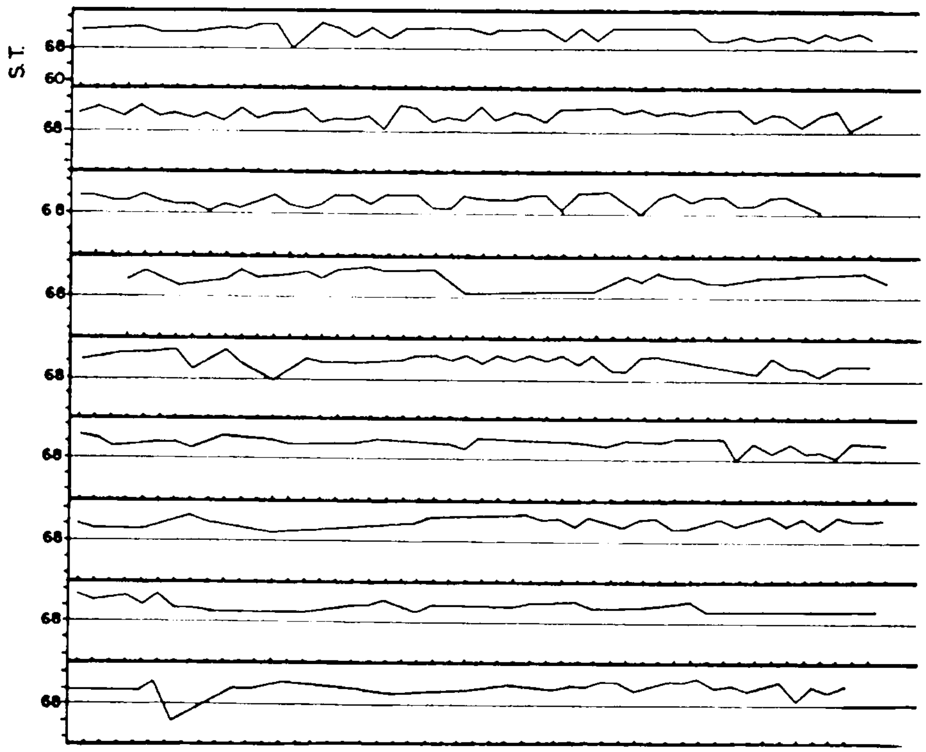

FIG. 49. The urinary *surface tension* remains constantly fixed *above* the average value of 68 for more than a year in a case of cancer of the urethra.

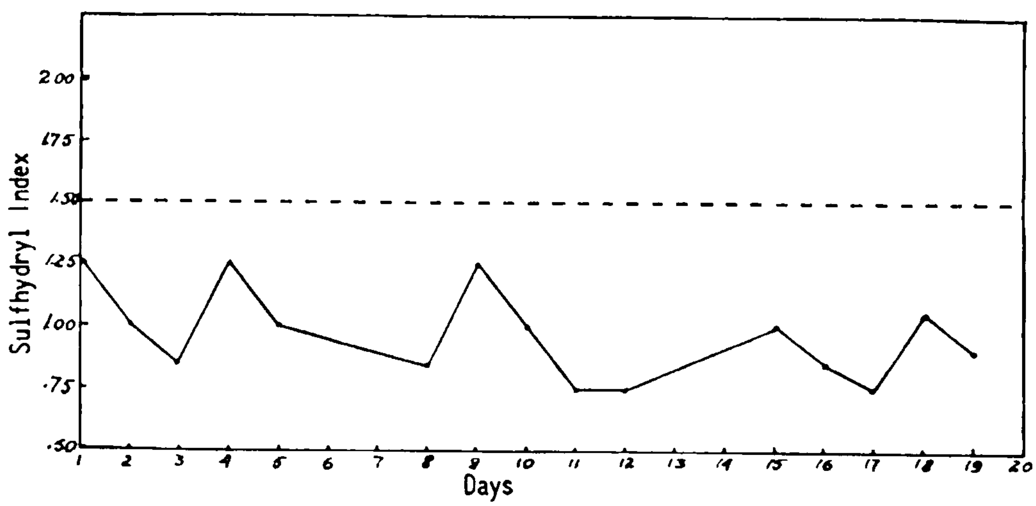

FIG. 50. The urinary sulfhydryl index remains below the average value of 1.5, in a case of cancer of the breast, with bone metastases.

It was especially in advanced stages that definite groupings of patterns with opposite characteristics could be recognized. They corresponded to two fundamental offbalances which we have called "Type A" and "Type D." ("A" for anoxybiosis, "D" for dysoxybiosis which represent the principal manifestations of oxygen metabolism in a phase of these offbalances.)

The correspondence between the different abnormal patterns defining the offbalance A or D, is seen in Figures 52 to 60. The abnormal pattern of

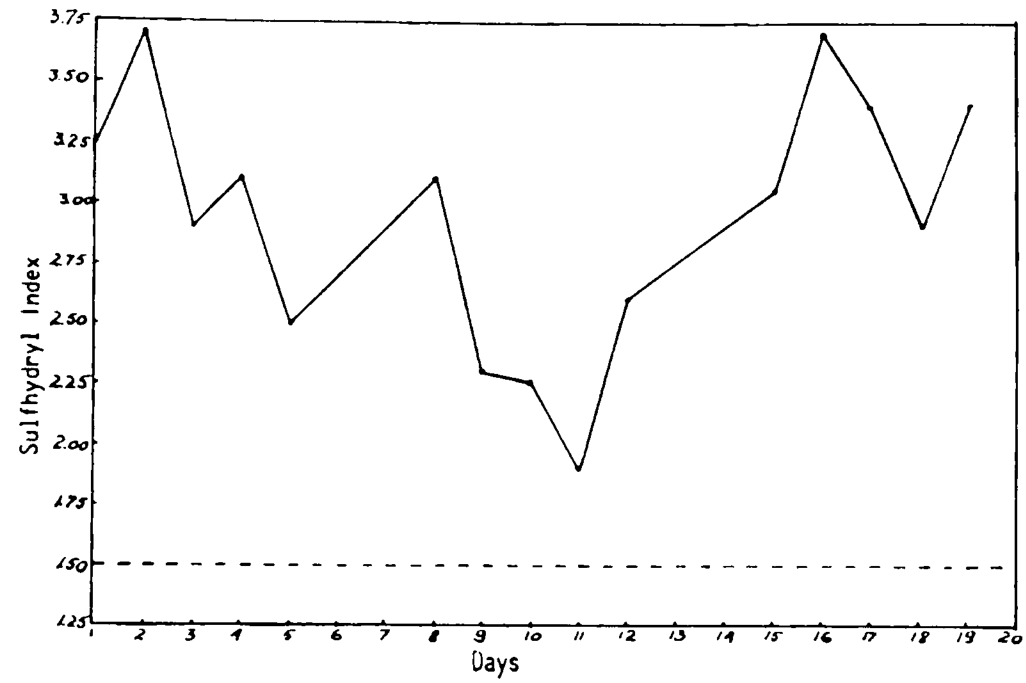

FIG. 51. The urinary sulfhydryl index remains above the average value of 1.5 in a case of hypernephroma with lung metastases.

the low urinary specific gravity appears together with a pattern of high values for the pH, both corresponding to the offbalance type A. *(Fig. 52)* A high urinary pH and low chloride index pattern correspond to the offbalance type A, as seen in Fig. 53. The analyses of a case with low specific gravity, high pH, low chloride index and high surface tension, as present in offbalance type A, is shown in Fig. 54. An opposite case, offbalance type D, with high specific gravity, low pH, high chloride index and low surface tension is shown in Fig. 55. A similar case of offbalance type D is shown in Fig. 56 with high urinary specific gravity, low pH, low surface tension and low blood leucocyte number. In Fig. 57, the low pH, high sulfhydryl index and low surface tension show an offbalance of the type D.

The independence of the levels may explain why, in the same subject,

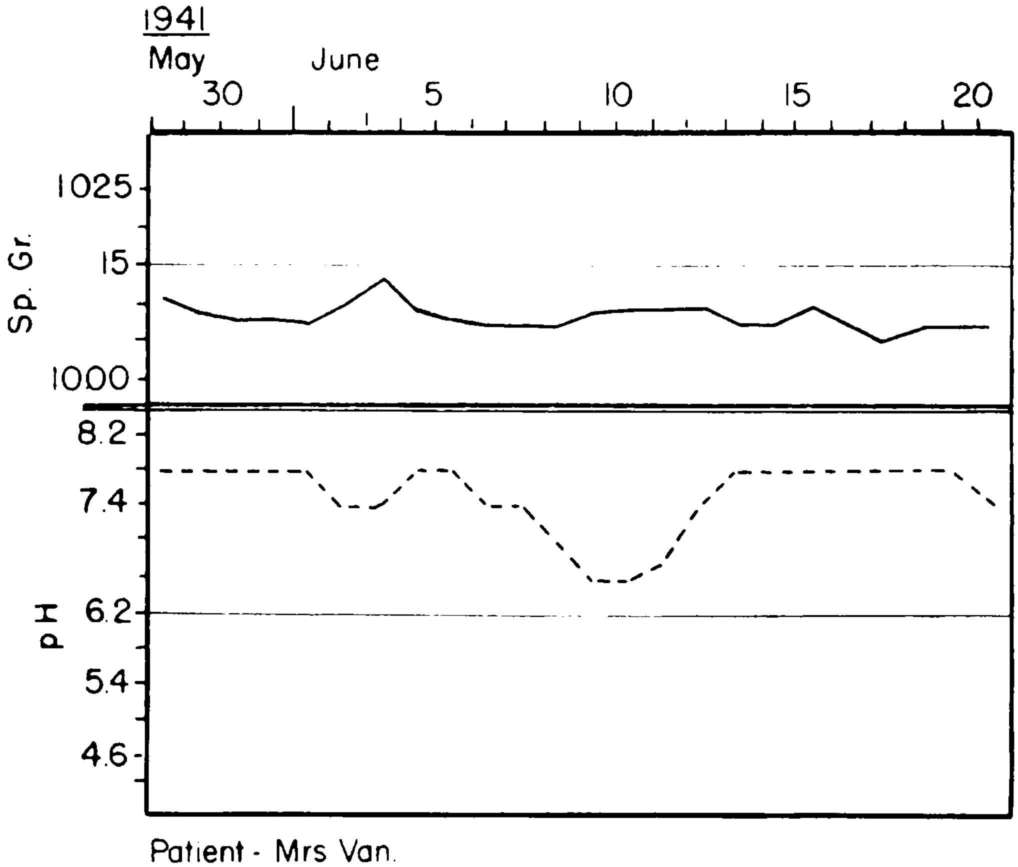

FIG. 52. A correspondence is seen between the patterns of *urinary specific gravity* and that of the *urinary pH* in a cancer of the colon corresponding to the type A offbalance. The changes still present in the curves are opposite.

not all the analytical patterns obligatory concord at all times in the same subject. Especially when defense reactions intervene, the offbalance at one level can be different from that at other levels. Fig. 58 shows such examples. Usually, as the disease progresses, many of these differences disappear, the manifestations—analytical and clinical at different levels—entering in the same type of offbalance. Fig. 59 shows such an example.

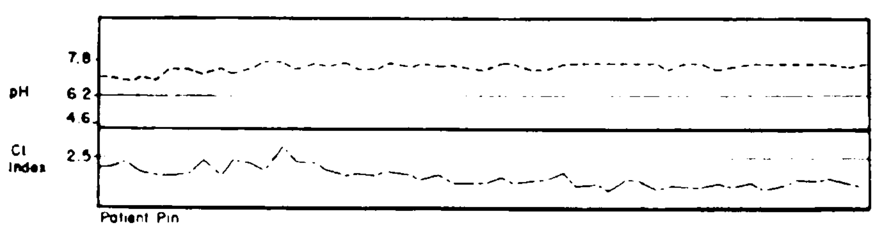

FIG. 53. In a case of sarcoma of the leg with lung metastases the curve of the *urinary pH* is fixed above the average line (6.2) while the curve of *chloride index* below the average line of 2.5. This relationship indicates a type A of the offbalance.

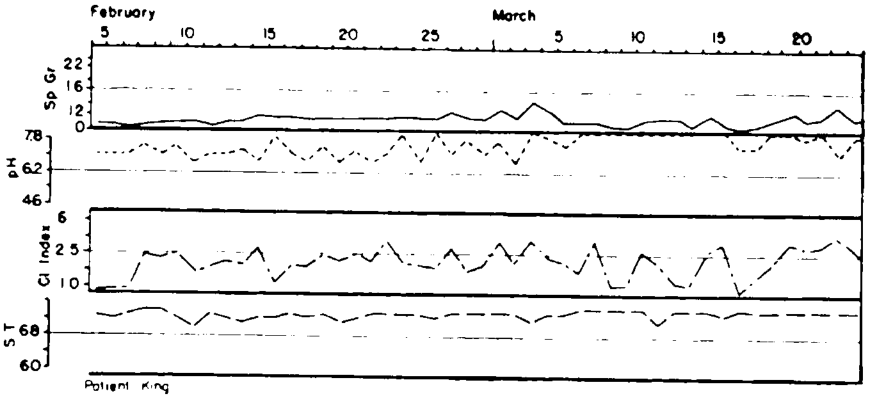

FIG. 54. The analysis of a terminal case of cancer of the breast, showing the *fundamental offbalance,* low specific gravity, high pH, low chloride index and high surface tension, corresponding thus to the offbalance A.

The passage of a subject from one offbalance into the opposite one is seen to occur during the evolution of the condition most often induced by therapeutic attempts. Fig. 60 shows such an example.

The two opposite offbalances, identified first through the urine analyses, could be recognized to exist for all the manifestations taking place at the different levels of the organization. The manifestations seen at these levels could thus be interpreted as corresponding to one of the two opposite fundamental offbalances, type A and D. Table IV shows this coordination of the different manifestations according to the two opposite offbalances.

On the basis of all these data, clinical manifestations and analyses, the dualistic pathogenic concept appeared to be well established and the dual-

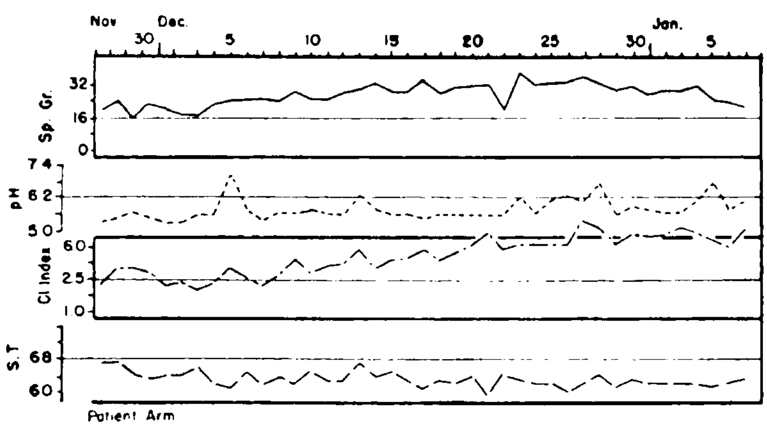

FIG. 55. A terminal case of cancer of the breast shows all the analyses fixed in opposite position to the case of Fig. 54, i.e., high specific gravity, low pH, high chloride index and low surface tension, corresponding to an offbalance of the type D.

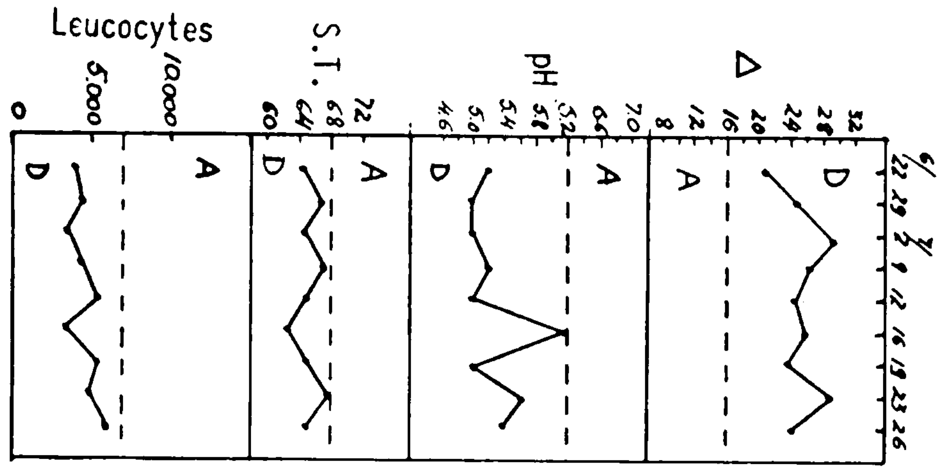

FIG. 56. Offbalance type D, shows high urine specific gravity, low pH, low surface tension and low blood leucocyte number.

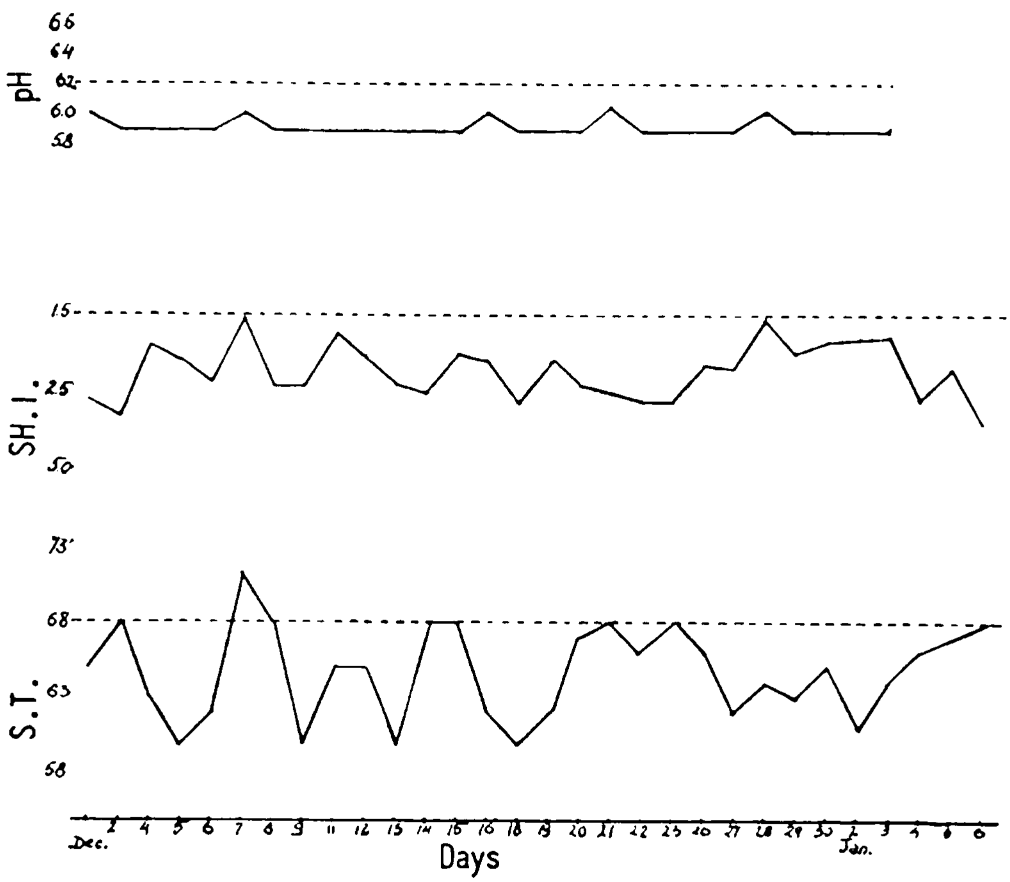

FIG. 57. The 3 curves, pH, sulfhydryl index and surface tension show an offbalance type D.

istic physiopathological mechanism studied in complex conditions in general and in cancer in particular.

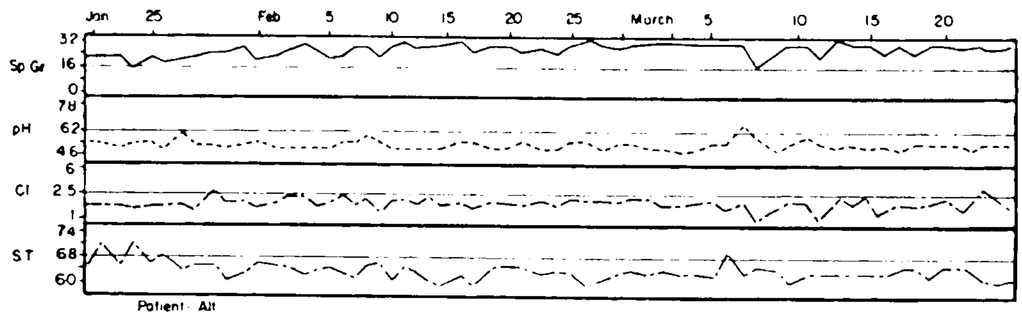

FIG. 58. The urine analyses of a patient with cancer of the ovary, showing a discordance between the patterns present. While all the analyses show patterns of the type D, the chloride index remains throughout the entire observation constantly of type A.

Place of Dualism in Cancer Physiopathology

After recognizing a dual pattern in most manifestations of cancer, the problem was to consider the relationship between this dualism and cancer itself.

One critical observation was that a pattern in a given patient may change. During the evolution of the condition, seldom is the change from abnormal to normal, but usually from one abnormal to the opposite abnormal pattern. This fact has a special importance as will be seen later. In some cases, even the immediate, direct cause of such changes could be established.

The following case is illustrative.

Mr. S. L., a patient with cancer of the prostate and metastatic destruction of half of the sacrum, was in very severe pain. Study of variations in pain intensity and in urinary pH, as well as the response to acidifying and alkalinizing substances, indicated that the pain was of a typical acid pattern. The patient started radiotherapy and pain decreased with almost every treatment, until after a few sessions it had disappeared completely. Out of bed and feeling well, he continued the treatment. However, at about the twelfth session, pain again appeared and thereafter increased with each treatment. After five more sessions, he was back in bed and suffering such unbearable pain that radiotherapy had to be discontinued. At that time, a new analysis of the pattern of pain showed that it had changed from the original acid to alkaline. It was hypothesized that this change might be the

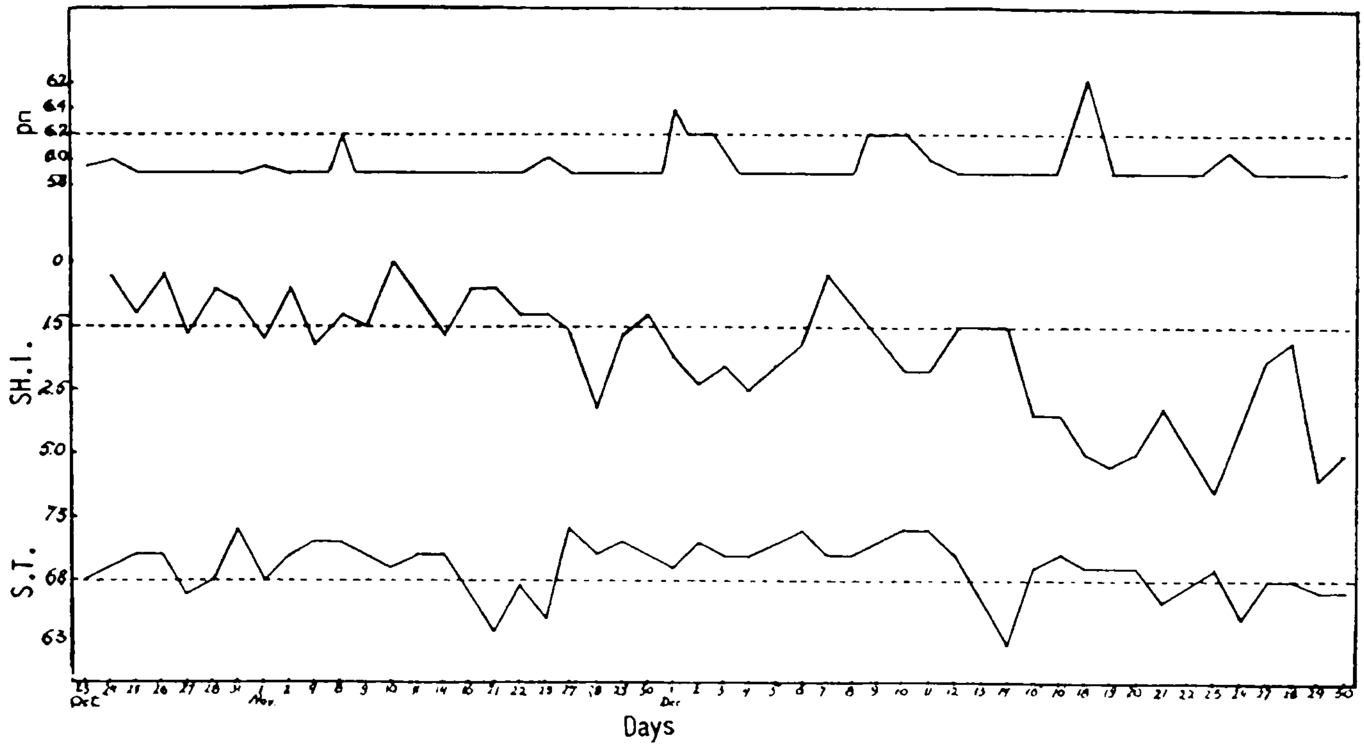

FIG. 59. The passage of discordant patterns into their opposite patterns, in order to realize a concordant offbalance as seen in a case of cancer of the stomach. At the beginning of the observation, low pH values show a pattern corresponding to type D, while two other analyses—sulfhydryl index and surface tension—are of offbalance A. With the progress of the condition, sulfhydryl index and surface tension values pass gradually from offbalance A also to offbalance D.

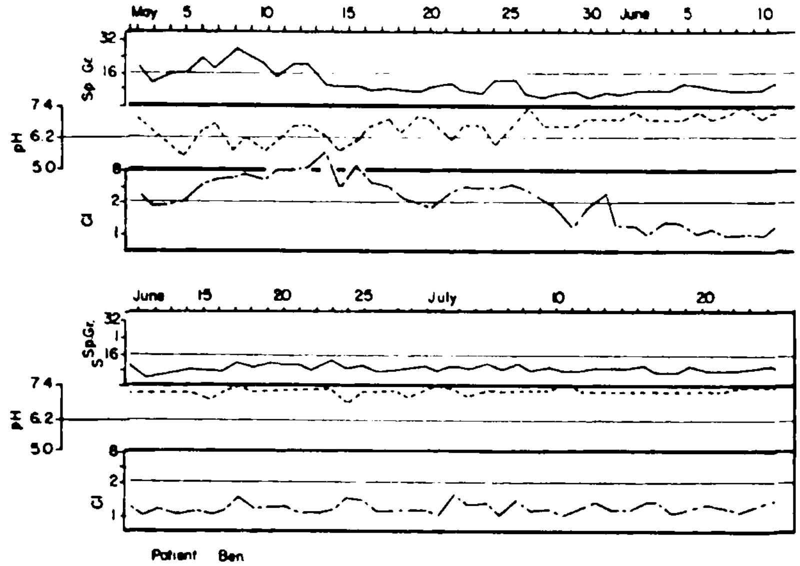

FIG. 60. A condition can pass from one offbalance to the opposite one. *The passage of the analyses from the offbalance type D into the offbalance type A* is seen in a case of cancer of the lung. The analyses which first show high specific gravity, low pH and high chloride index, pass subsequently to the opposite side, with low specific gravity, high pH and low chloride index. This new offbalance remains unchanged for a long time as shown in the second part of the curve.

result of irradiation. Study of other cases, after irradiation, has confirmed the hypothesis.

Changes of pain from an acid to an alkaline pattern also were observed in patients who had suffered shock or serious pyrogenic infections. Viral infection such as flu, or even smallpox vaccination, seemed to induce an opposite change—from alkaline to acid. Changes obtained under the influence of therapeutic agents were frequently observed and will be discussed later.

The dual pattern seen for most cancer manifestations was integrated into the concept of the disease as a complex organized condition that develops through progressive participation of hierarchically superior levels of the organization. From a clinical point of view, such participation corresponds to the successive addition of new manifestations to a previously less complex condition. According to their levels, these "Added Factors" correspond to prolonged youth or rapid cellular aging, to acid or alkaline pain, to blood and urinary analytical data fixed in one or another of two opposite patterns. Dualism is the principal characteristic shared in common by all these progressively added manifestations.

In trying to understand this dualism and its significance, we had to consider again the place of dualism in the general organization of nature. The study of reactivity in nature has led to the recognition that a basic dualism exists—that the forces operating in nature can be separated into two opposite groups for almost all the intervening factors. Forces which would tend to lead toward annihilation of differences and produce a state of maximum entropy or homotropy or the antagonistic forces which tend

TABLE IV

MANIFESTATIONS

Level	Offbalance "A"	Offbalance "D"
Cellular	Prolonged cellular youth Less differentiated cells, especially of connective tissues Increased amount of connective tissue	Rapid cellular aging More differentiated cells, especially of connective tissues Decreased amount of connective tissue
Tissular	Increased lymphatic tissue Low oxido-reduction potential processes Low chloride content Local acidosis Acid pattern symptoms (Pain, dyspnea, itching, etc.)	Decreased lymphatic tissue High oxido-reduction potential processes High chloride content Local alkalosis Alkaline pattern symptoms (Pain, dyspnea, itching, etc.)
Organic	Somnolence Constipation Polyuria Exophtalmia Nasal pH below 6.5 Slow absorbtion of skin wheal	Insomnia Diarrhea Oliguria Enophtalmia Nasal pH above 6.5 Rapid absorbtion of skin wheal
Systemic	*Blood* Leucocytosis Eosinophilia High color index Low potassium content Low R.C. sed. rate No C reactive protein *Urine* Low specific gravity High pH High Cl, Na excretion Low SH, Ca, phosphate, sulfate excretion High surface tension Death in coma	*Blood* Leucopenia Eosinopenia Low color index High potassium content High R.C. sed. rate High C reactive protein *Urine* High specific gravity Low pH Low Cl, Na excretion High SH, Ca, phosphate, sulfate excretion Low surface tension Presence of oxidizing substances Death while conscious

to maintain and increase differences and lead to more complex organization —and are thus catalogued as negatively-entropic, ectropic or heterotropic —would thus appear with each new added factor when a higher hierarchic entity is realized. For this reason, they will appear especially manifest for the same added factors intervening under abnormal conditions. Dualism consequently concerns the manifestations progressively added. The result is seen in the alteration of the oscillatory movement with alternate predominance of one and then the other of the antagonistic forces for these added factors. This fact would explain the dualism seen especially in abnormalities. It also explains the intervention of the dual patterns mentioned above.

Dualism becomes even more important when it can be seen to play a capital role in the mechanism through which agents act upon abnormal conditions. Originally, the dualistic actions of agents could be ascertained through the changes induced in pain and various other patterns. It has consequently been possible to classify the effect of various therapeutic agents according to their influence upon these patterns and, through this more readily measurable influence, on the fundamental offbalances themselves.

At the same time, the study of the influence exerted by various agents upon these patterns, which is presented later, has posed the problem of precisely what effects upon these patterns are produced by the substances which are body constituents. And this led us to a third basic concept dealing with the important role played by body constituents and, in particular, by the lipids.