CHAPTER 11

THEORY-FORMULATION IN MEDICAL SCIENCE

The important thing in science is not so much to obtain new facts as to discover new ways of thinking about them.

William Lawrence Bragg

BACKGROUND

The primary purpose of this book has been to develop a theory on the relationship between stress and disease, put forward previously only in outline. A second and no less important aim has been to analyze current methods of theory formulation in medicine, and this chapter is devoted that.

The major area of disease pathogenesis I wish to discuss is where we already have a good body of evidence available, but without firm conclusions - other than descriptive labels, such as sarcoidosis, fibrosing alveolitis, benign intracranial hypertension, etc. If we can develop some simple few simple guidelines, we should be able to advance our understanding of such diseases. Even where no final formulation can be synthesized, we should at least be able to ‘corner’ our understanding at any stage during the accumulation of the evidence, so as to point more appropriately to future research directions.

The importance of theory formulation in medical science cannot be over-emphasized, yet it has not been well studied. Most investigators proceed on the basis that as long as their experiments are well conceived and well planned, more data collection is usually all that is needed. And there is no doubt that in these days of such breath-taking technology the information collected can be very impressive indeed. What we need to remember, though, is that all data is “theory-infected.” This is so not only in the sense that data is always interpreted in the light of existing theory, but in that the very data collected, the very experiments performed, are strongly influenced by views underlying causation. Failure to appreciate this may not be of great importance in what Thomas Kuhn called the ‘normal’ periods of science, where existing theoretical concepts remain valuable as a working heuristic. But so often in medical science this is not the case, and then theories can lag far behind
the process of data acquisition, sometimes to the extent that they eventually become entirely outmoded and require something in the nature of a scientific ‘revolution’ to replace them. It is clear from this that we need a way of developing our theories dynamically over time so that they may lead and inform data collection rather than follow it.

It is surprising how few guidelines there are. This is understandable in fields where there is very little data available for synthesis, because then Popper’s views are entirely appropriate, namely that theory formulation is in the realm of the imagination, inaccessible to logical analysis and synthesis, and in his sense, metaphysical. But even there, we should be able to formulate some basic tenets, and a few have already been discussed in chapter 1, such as the virtue of simplicity, and of analogies or models borrowed from other fields of experience, in building new ways of seeing.

Even more surprising is that we have so few guidelines in areas where much data is already available. This was once the very home ground for operating Mills’ tenets of inductive reasoning. These have now been largely superseded, (see chapter 1) but very little has arisen to take their place. Popper (1972) has certainly given us some guidelines for assessing a theory after it has been formulated, such as its capacity to explain a wider body of evidence, and the ability to make better predictions, but that does not help us much to formulate the theory in the first place.

What we need is a method that allows us to build up theory from the data as it accumulates. This approach should be dynamic, so that the theory makes predictions and keeps ahead the data in an evolutionary way, so enabling us to avoid situations of revolutionary change where the baby is thrown out with the bathwater. An example can be seen in the controversy that surrounds the role of the recently (re-)discovered coronary artery spasm in the pathogenesis of coronary occlusion and myocardial infarction. Given the strong belief at the time that myocardial infarction was due to primary coronary thrombosis, it was hardly surprising to see a sharp polarization of views. But such polarization may miss the point, because coronary vasospasm and thrombosis could both be important, but at different stages of the evolution of the disease in time, for example by coronary vasospasm initiating a series of events which led to secondary coronary thrombosis. Whether this view itself is correct may be debatable, but I use it to illustrate how apparently conflicting new data can sometimes be embraced within a single theory built dynamically upon the old, as long as the situation is approached with new ways of seeing. Coronary thrombosis could supervene on primary coronary artery spasm (Ch. 3)

Perhaps an additional reason for this kind of black/white alternative theory framework is the strongly individualistic nature scientific investigators themselves, and their related drive to discover something fundamentally new and different. A complete break with the old gives a much more dramatic stance than some middle-of-the-road compromise, and also appeals as being more likely to lead to that much coveted journey to Stockholm. In my view, such factors are sometimes stronger than our supposed altruistic drive to discover a fundamental truth, and this is unfortunate, because it creates unnecessary conflict and leads to a discarding the lessons of history. Of course, new data
and new theory cannot simply be merged and absorbed into the old as if blotting paper, so what we
must try to formulate guidelines on rational ways of proceeding.

I will discuss those diseases where much data have already been accumulated but there is
conflict about underlying cause. This is by far the commonest situation in medical science. It has
been discussed and analyzed in part in chapter 2, but some of the conclusions drawn there warrant
brief recapitulation.

In chapter 2, I suggested that the general approach in this field should be first to sort the data
into sub-groups, and then draw initial sub-conclusions within each. Moreover, these sub-groups
should each address relatively independent categories of the data, and be such that when taken
together describe it all. In Medicine, the four suggested categories were, Anatomical, Pathological,
Functional and Aetiological diagnoses. This process can make difficult data much easier to
assimilate and analyze. In its absence, the wealth of available data can often threaten to overwhelm
the capacity of the individual mind to interpret it, particularly in these days when super-specialization
means that only certain facets of the data can be thoroughly understood by any one investigator.
Such specialization is unquestionably valuable, but it makes it even more important to try to
formulate general ground rules for understanding.

The next important step in defining disease causation is to separate off those aspects that can be
relegated purely to the Functional category of diagnosis (i.e., purely as secondary consequences of
the disease process), because this narrows down the amount of data we have to consider in relation
to underlying cause. But, even here, we have to be careful, because some of the more obvious
secondary consequences of organ disease may feed back upon and eventually influence disease
causation, and quite profoundly so.

THE CHAIN OF MECHANISM IN DISEASE CAUSATION

Many practicing medical scientists hold that there cannot really be any logical process to theory
formulation at all, and prefer to wait for the occurrence of some "Eureka" act or the dawn of Popper's
‘Third World’ for insight and enlightenment. Those who do believe that we can make rational
interpretations of the data tend to fall into two separate categories, — the ‘splitters’ and the ‘lumpers.’
The splitters try to solve the problem by holding that causation is multi-factorial. The lumpers or
reductionists, on the other hand, look for some underlying mechanism that they can relate to disease
cause, and then regard all other aspects as being of lesser importance. Both approaches can contain
an element of truth, but in my view each in its simplest form is insufficient. In one sense, the multi-
factorialists merely state the obvious. No one can deny that there are often many factors involved in
disease causation, but to simply say that disease is multi-factorial is not really to put forward a
scientific theory at all, unless there is some concurrent statement of how the different factors fit
together. Otherwise, such theories tend to become all things to all men and, for example, Page's
mosaic theory of hypertension causation\textsuperscript{11} is very suspect on these terms. The reductionists, on the other hand, often seem to go too far the other way. At least those who might be referred to as "naive reductionists" often seem to make several unwarranted assumptions. The first is to assume that there is a direct and immediate connection between underlying cause and effect manifesting as the disease. This ignores the likely importance of mediating factors in what we can might the chain of mechanism over time. For example, most of the studies on the relationship of various carcinogens to lung cancer have been done at the cellular level, on the tacit assumption that the chemicals concerned damage the cell (DNA) by a direct toxic action.\textsuperscript{12} But to assume this is to neglect the potential importance of physiological and other mediating mechanisms along the way. Thus, it is at least theoretically possible that the chemicals involved (e.g. nicotine) act in vivo by impairing bronchial mucosal blood flow with resultant indirect cell damage, rather than by a direct toxic carcinogenic effect. Similarly, the propensity of oral contraceptive steroid therapy to cause arterial thrombosis has often been assumed to be due to a direct biochemical action on blood coagulation and thrombotic mechanisms. Moreover, much evidence has been adduced for the occurrence of such changes. However, it would seem wise to entertain the possibility of a less direct relationship between initiating steroid cause and eventual thrombotic effect, particularly in view of the observation that many of the thromboses are anatomically of such a localized nature. And this approach can give an interesting new way of seeing. For example, patients on oral contraceptive therapy often show the side-effects of Raynaud's phenomenon and migraine, both vasospastic disorders, so the question arises whether the steroid action precipitating and localizing thrombosis could be a sensitization of the relevant arteries to spasm, with thrombosis being secondary to that (also see Ch. 6). The latter view may reveal my own bias, but I put it forward more to show how the link between underlying biochemical abnormality and actual disease state can be much more indirect than we generally suppose. Perhaps a more subtle example is in the way alterations in sodium transport are viewed in relation to hypertension. Such defects are thought by some to be the fundamental abnormality underlying the high blood pressure.\textsuperscript{13} Whether this is so is debatable, but the point here is that most who see it that way postulate a direct relationship of cause to effect. They assert that the sodium pump abnormality causes hypertension by acting directly to alter vascular smooth muscle reactivity to vasoconstrictor stimuli. Very few have entertained the possibility of a more remote connection, perhaps one removed by many biochemical and/or physiological steps. Folkow is one of the few,\textsuperscript{14} and he proposed that the important aberration produced by the sodium pump disturbance could be more in the realm of increased sympathetic nervous system output, even perhaps at the level of connections in the mind subserving the patient's cardiovascular reactivity to stressful stimuli.

Another problem with the reductionist approach is that it far too often assumes the basic defect is indeed biochemical or molecular. In the most fundamental sense, of course, this must be true, because we are undoubtedly composed of molecules. But we are not just molecules, and given the limited information we have about some diseases, perhaps the best way to start understanding them
is first in physiological terms. For example, morbid obesity is usually assumed to be a ‘metabolic’ disorder, stemming from a basic biochemical defect. But progress so far towards understanding the condition on that basis has been very slow, and it might be interesting to take an alternative physiological approach. Along these lines, we might ask whether the obesity could be related to a lowered set-point of body temperature, with the resultant lower rate of basal metabolism allowing more of any given caloric intake to be diverted from energy utilization to energy storage. In this respect, it is interesting to note that non-shivering thermogenesis from the metabolism of brown fat is indeed reduced in response to cold in some patients predisposed to obesity.\textsuperscript{15} I do not put forward this view as a definitive statement on obesity causation, but to illustrate that if we want to understand that condition, physiological modeling can be just as important as biochemical.

Actually, even when a molecular disturbance is discovered in any disease state, there is no reason why it should be seen as the fundamental underlying stimulus, because it could merely reflect one of the mediating factors along the chain of mechanism. An example of this can be seen in Parkinson's disease, where there is known failure of dopamine production within the neurogenic pathways of the midbrain, and one which can be dramatically improved by the administration of the compound L-dopa. However, this should not be taken to imply, as it sometimes has, that this is the basic biochemical abnormality. Indeed, it probably is not. Parkinson's disease tends inevitably to progress long-term despite treatment with L-dopa,\textsuperscript{16} and it seems more likely that its fundamental cause is related to whatever induces this local area of the midbrain to undergo a process of atrophy over time. In that light, progressive impairment of this dopamine pathway may be seen as a secondary phenomenon, and L-dopa ameliorating it for a time merely as ‘flogging a tired horse’. Clear-cut biochemical defects need not necessarily be primary.

Of course, physiological modeling of disease is not necessarily less complex than biochemical. Indeed, it can initially complicate rather than simplify the picture. For example, high alcohol intake is associated with hypertension,\textsuperscript{17} and whilst it may be true that the biochemical approach has not much helped understand the nature of this association so far, if we take the alternative physiological view, a real paradox arises: the direct physiological effect of alcohol on the circulation is to reduce blood pressure by vasodilatation.\textsuperscript{1} Despite this, pursuit of the physiological is worthwhile. Thus, alcohol can have profound withdrawal effects, with a secondary increase in sympathetic nervous activity. So the connection might be a vasoconstrictive one related to withdrawal as a rebound phenomenon.\textsuperscript{18} In a similar way, understanding the side effects of medications in physiological terms might perhaps give important insight into some disease states, e.g. hydrallazine-induced vasculitis as a possible model for the study of systemic lupus erythematosus. In that respect, the drugs that induce lupus also happen to be vasodilator agents, so again one might ask whether rebound vasoconstrictive ischaemic cell (DNA) damage could be part of the stimulus underlying the disease.

THE DYNAMIC NATURE OF THE CHAIN OF MECHANISM
It might be said that there are many ‘enlightened reductionists’, molecular and otherwise, who are well aware of the existence of a chain of disease mechanism in disease causation. But they usually see such relationships as being relatively static, and this is not necessarily so. The multi-factorialists, on their part, so often see the situation as one where the different factors are more active in different sub-populations of patients with the disease. It is in this sense that I believe both the strict reductionists and the multi-factorialists often miss the point. What one sees strikingly as a clinician is that different among the multiple factors along the chain of mechanism can come to dominate disease causation differently at different stages during the evolution of any disease over time, even within the single individual. To illustrate, I will look at some aspects of the inter-relationship between cause and effect in biology.

CAUSE AND EFFECT IN BIOLOGY

In the sphere of logical argumentation of the type expounded by Mill (1906), cause and effect are separate, and their relationship unchanging. But in the scientific world, things are often very different. Even in physics, what one sees as cause, and what as effect, may depend very much on the point of view one takes at any given time, as so well illustrated as long ago as 1920 by Campbell in discussing Hooke’s Law of the relationship between the extension of a solid and the amount of force applied. In biology, the relationship between cause and effect can be even more complicated, and at several levels.

The easiest level to understand is the physiological. There, we are familiar with the concept that the effect of a stimulus can have a feedback influence on cause. This is seen, for example, with suppression of endogenous mechanisms normally maintaining blood pressure when exogenous hypertensive agents are infused in vivo. In a stable physiological system, most feedback influences of this type are negative. Physiological feedback processes continue to operate in disease, as in the suppression of renin secretion in some patients with essential hypertension. Such influences are important in understanding disease causation. First, by suppressing the initiating stimulus, negative feedback processes can make the search for underlying causative mechanisms much more difficult. Second, any positive feedback effects arising in disease can come to amplify underlying causation over time. For example, acute ‘heart attacks’ are frequently associated with severe pain, anxiety, and hyperventilation, and if, as has been argued in chapter 3, the whole process is triggered by coronary artery vasospasm, then such factors might well feed back upon and greatly amplify the underlying vasospastic stimulus (e.g. by activating sympathetic nervous vasoconstrictor outflow to the coronary arteries &/or reducing arterial pCO2 etc.).

The major point I wish to make in relation to disease, though, is that with the passage of time, even those effects which begin purely as consequences of the underlying stimulus, may eventually
come to be largely responsible its maintenance in the chronic state. An example comes from an earlier chapter (Ch. 4), where we saw how repeated focal coronary artery vasospasm could cause local wall injury, and hence the gradual build up of the atheromatous plaque, so that structural arterial narrowing eventually came to replace the functional. A similar example comes from spontaneously hypertensive rat model, where the initial elevation in blood pressure appears to be episodic and related to an exaggerated and transient arteriolar vasoconstrictor response to stress, but over the weeks a secondary structural arteriolar narrowing comes to replace the functional in much the same way as above, to dominate the hypertension in the chronic phase.

These examples illustrate how disease might often be multi-factorial in a new and importantly different sense, namely multi-factorial in time, in that the various mediating factors along the chain of mechanism can have secondary effects that come to dominate later cause.

**PATHOLOGY AS AN EXTENSION OF PHYSIOLOGY IN TIME**

The foregoing hints at another important principle, namely that in some diseases the established pathological state might be the end-consequence of an exaggerated or prolonged physiological stimulus over time. In the spontaneously hypertensive rat, for example, the initial stimulus to the elevated blood pressure seems to be a greater-than-normal cardiovascular pressor response to stress. But as the weeks go by, the physiological seems gradually to give way to the pathological, as functional arteriolar constriction is replaced by structural arteriolar narrowing from lumen encroachment and pathological change. In the same vein, the early phase of coronary artery disease might reflect focal and episodic physiological constriction from stress. But as each episode causes increasing arterial wall damage, functional narrowing is replaced by structural atheroma, so that the physiological process merges into the pathological disease state.

There are other examples of this. Physiological hyperplasia of the thyroid gland often occurs in individuals living in iodine-deficient areas, and leads to thyroid swelling or goitre. In its initial phases this is due to thyroid hyperplasia as a physiological response, and one where feedback mechanisms are intact. However with the passage of time, the goitre gradually becomes more nodular and irregular i.e. shows clear-cut pathological changes. Essentially, a pathological state has arisen as an extension of physiology over time. The gland now shows deranged behavior in the functional sense, in that thyroid hormone production becomes relatively independent of iodine intake, i.e. autonomous. The latter point can be demonstrated very dramatically when such patients are given iodine replacement therapy after many years of goitre, because the enlarged thyroid gland may then produce uncontrolled amounts of thyroid hormone to induce a state of thyrotoxicosis as so-called Jod-Basedow phenomenon. The gland at this stage has escaped the normally well-regulated negative feedback influence of iodine levels on thyroid hormone production. Clearly, there is now a pathological state from the standpoints of both function and pathology.
The field of endocrinology supplies other examples. One relates to parathyroid gland hyperactivity in renal disease. In many forms of chronic renal impairment, the kidney lacks the capacity to activate vitamin D to its biologically active form, and a fall in plasma calcium ensues. This, in turn, stimulates the parathyroid gland to produce parathyroid hormone in a compensatory way, so tending to bring the plasma calcium back towards normal. No doubt this sequence of events is initially entirely physiological, but with chronic stimulation the parathyroid gland can develop clear histopathological changes, and also function autonomously. Thus, from beginning as a purely compensatory hyper-parathyroidism secondary to a lowered plasma calcium, the final state sees an autonomous pathological parathyroid gland causing an elevation of serum calcium well above the normal range (‘tertiary’ hyper-parathyroidism). This can become particularly evident after renal transplantation, because then the continued functional autonomy of the abnormal parathyroid gland can then lead to severely elevated parathyroid hormone and hypercalcaemia despite normalization of vitamin D activation, i.e. despite removal of the originating stimulus.

THE BORDERLAND BETWEEN PHYSIOLOGY AND PATHOLOGY

The above examples have illustrated how some diseases may begin as a physiological response and gradually merge into a pathological state as the stimulus is continued over time. In the early phases, the situation is entirely physiological, with normal functional feedback mechanisms preserved and no histo-pathological abnormalities. In ‘end-stage’ disease, feedback becomes quite deranged and pathological changes come to dominate the picture. What it now important to recognize is that, in between these extremes, there is often a borderland which is neither physiological nor pathological and about which, not surprisingly, much confusion arises. For example, early in spontaneous hypertension in the rat, any elevation in blood pressure seems to relate to exaggerated responses to stressful physiological stimuli. In its chronic stages, however, the picture is dominated by structural vascular narrowing of a quite pathological type. But, in between, there is an increase in arteriolar medial smooth muscle cell bulk which can be seen as "hypertrophy" or "structural adaptive" process if one is of physiological bent, or as early pathological change if one's inclinations are more in the direction of pathology.

It might be thought that the true situation could be established by determining the degree of reversibility after the stimulus was withdrawn. But this is not necessarily so, because that presupposes physiological changes to be rapidly reversible and pathological ones fixed; although the former is generally true, there is no reason why early pathological change should not be reversible. One can imagine, for example, that the pathological changes within the arteriolar wall in hypertension might include oedema formation and fluid insudation, both of which might largely regress after the episode of transient hypertension had passed. Structural abnormality in this intermediate phase
should not necessarily be equated with irreversibility, and reversibility should not be taken to imply that the underlying mechanism is entirely physiological.

There is yet another important element to this borderland between the normal and the abnormal. Many diseases, particularly vascular ones, are not clear-cut entities at all, but merely extreme ends of a normal distribution spectrum within the population. As such, they should be regarded more as diseases of quantity than quality, and therefore have something to tell us about normal bodily processes. Hypertension, for example, produces accelerated vascular and ‘end-organ’ ageing, and as such its study could shed a great deal of light on the normal ageing process. As in so many areas, the present study of ageing tends to be dominated by biologists at the molecular and cellular level looking for specific abnormalities. But from the perspective of all the vascular pathology we see in the normal ageing population, the wonder is, by contrast, that anyone should ever reach beyond three score years and ten.

**THE DYNAMIC NATURE OF PATHOLOGY IN TIME**

The foregoing has given an indication that pathophysiology may be a very dynamic process. The point I want to emphasize now is that even in the later stages of disease, when the histo-pathological picture has become quite abnormal, and control mechanisms grossly deranged, we should still not assume that all is totally irreversible from either the structural or functional standpoint. An example of this can be seen in chronic essential hypertension where long-term reduction of a chronically elevated blood pressure by anti-hypertensive agents may lead to the partial reversal of what have been hitherto considered “fixed” structural arteriolar changes. Even proliferative inflammatory changes are to some extent reversible.

An important corollary is that if we do wish to discover the basic abnormality underlying or initiating much disease, we should not only take a physiological as well as biochemical view, but we should examine the condition at a very early stage during its development in time. Perhaps a good example of this again comes from the field of essential hypertension in man, where the long-standing and strong suspicions that an increased sympathetic nervous activity plays a primary role have so far been very difficult to confirm. It is interesting in the present context that younger patients seem to show most evidence of increased sympathetic nervous activity. Sympathetic denervation for resistant hypertension might therefore have best results if done relatively early in the course of the disease.

**THE AETIOLOGICAL BASIS UNDERLYING DISEASE**

Once we have characterized the type of physiological dysfunction associated with any disease,
we will want to go on to discover the nature of the underlying aetiology. This may be an exaggerated response to entirely normal stimuli or a heightened stimulus from the environment itself. Such factors may be important even in cases with a clear hereditary component to the disease, particularly where the onset of clinical manifestations is delayed until adult life (e.g. in Huntington's chorea). Important environmental stimuli in this respect could either be of a physical or psychological nature. Environmentalists and epidemiologists may be persuaded of the importance of pollution and nutrition as well, but as a clinician one cannot help being impressed by the amount of psychological stress there often is in the background to disease.

When we do find a component of increased response to the environment, our next task should be to go on and determine the level at which this occurs. For example, in the spontaneously hypertensive rat the early-phase elevation of blood pressure is associated with an exaggerated vasoconstrictor response to stress. But having discovered that, we then need to examine whether this is due to an exaggerated response of the arteriolar smooth muscle cells to a normal sympathetic vasoconstrictor outflow, or a hyper-responsiveness along some part of the sympathetic pathway stimulating it. In this sense, we should always be driven back to questions that may be currently unanswerable.

THE POSSIBLE SCOPE OF VASOSPASM IN CAUSING DISEASE

Much of the thesis put forward in the present monograph, particularly that in Part 1, has emphasized how arterial vasospasm, especially focal vasospasm, might provide a basis for much stress-related disease. There are several general points that arise from this. First, if vasospasm is so important, why is it so frequently so focally distributed along the arterial lengths? That could be due to focal irregularity in the distribution of nerve endings to different sections of the artery, or focal receptor-clustering, or even of focal differences in vascular smooth muscle response from site to site along the artery. As well as being focalized in space, vascular spasm is very frequently localized in time, as in the propensity for Raynaud's phenomena and migraine to be first manifest around the time of adolescence.

Finally, I indicate general situations where vasospasm is likely to contribute to disease pathogenesis. The strongest contexts, almost the ‘full house’ as it were, is as follows:

(i) Where the disease is anatomically distributed in a focal way related to some aspect of vascular blood supply.

(ii) Where pathologically there is evidence of localized atrophy.

(iii) Where functionally the derangement is greatly out of proportion to the degree of pathological change, at least in the early phases and

(iv) Where aetiologically, psychological or physiological stress are prominent in the background. Short of this, wherever we find some of these aspects in isolation, without adequate explanation,
the possibility of a vasospastic contribution to pathogenesis should be considered. Anatomically sharply-localized disease is a case in point, as in Crohn's disease, where normal and diseased gut mucosa may be found within a few millimetres of each other. Pathologically, any evidence of atrophy, especially localized atrophy should also arouse suspicion of underlying repetitive ischemia. This is particularly so in the central nervous system, because neurones are so exquisitely sensitive to lack of blood supply that they might well be damaged by even quite-transient episodes of ischemia. It might well be useful, for example, to consider senile dementia from this perspective – as repeated neuronal damage from minor episodes of ischemia. That is for future analysis.

CONCLUSION

In this chapter, I have tried to indicate some aspects of disease causation observable from the standpoint of a clinician, yet little considered to date by medical science, and with so little influence on the current philosophical of our approach to understanding disease causation. I hope to have persuaded the reader that a dynamic evolution of disease through a series of changing pathophysiological mechanisms over time is worthy of consideration, and that the general guidelines for theory formulation in medicine can be useful in developing models for understanding disease. In the final analysis, as much as it has tried to put forward new concepts on disease, this monograph has been concerned with finding new ways of seeing so that we might formulate concepts and models about it, particularly in areas where current theories are clearly deficient. If I have achieved some small advance in that respect, I shall be content.

REFERENCES

    vasospasm as a possible cause of myocardial infarction. A conclusion derived from the study
11. Khosla MC, Page IH, Bumpus FM. Interrelations between various blood pressure regulatory
13. Sever PS, Poulter NR. A hypothesis for the pathogenesis of essential hypertension: The
15. Jung RT, Shetty PS, James WP, Barrand MA, Callingham BA. Reduced thermogenesis in
17. Criqui MH, Wallace RB, Mishkel M, Barrett-Connor E, Heiss G. Alcohol consumption and blood
    pressure and plasma angiotensin II concentration. A change produced by prolonged infusion
    64:273-80.
22. Clements FW. Goitre prophylaxis by addition of potassium iodate to bread. Experience in
23. Haussler MR, McCain TA. Basic and clinical concepts related to vitamin D metabolism and
24. Chatterjee SN, Friedler RM, Berne TV, Oldham SB, Singer FR, Massry SG. Persistent
25. Hallbeck M. Interaction between central neurogenic mechanisms and changes in cardiovasc
    ular design in primary hypertension. Experimental studies in spontaneously hypertensive rats. *Acta


