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READ BEFORE THE SCIENTIFIC SESSION

PRESIDENTIAL ADDRESS

SOME OF THE "DO'S" AND "DO-NOT'S" IN CLINICAL INVESTIGATION

BY FULLER ALBRIGHT

When your President and Council decided to hold this meeting, they had to ask themselves the following question put to them by the Office of Defense Transportation in Washington: Is this meeting likely to contribute to the over-all war effort? I, for one, and I think I speak for the majority of the Councillors, had no hesitation in answering the question in the affirmative. All knowledge is interrelated; in times of stress the most scientific nation has a big advantage. Surely a society like ours, where year in and year out some of the most important advances in medicine have first come to the light of day, should carry on through the present unpleasantness. Moreover, with so many of our colleagues scattered over the 7 seas, a big responsibility accrues to us who are left to keep the home fires burning in respect to clinical investigation.

It is perhaps a presumptive symptom of an oncoming intellectual menopause,—indeed, one might say it is evidence of a Young Turk becoming an Old Turk,—when one endeavours to lay down certain precepts for success in a field. It is probably fortunate that no one follows such precepts anyway, that each prefers to learn his own way, though this be the hard way. Be all this as it may, as I look around at those of our colleagues who have attained success in the field of clinical investigation and analyze what methods they have used, I see certain recommendations or "Do's" which may be worth jotting down; furthermore, as I look further, especially into my own past, I see certain "Do-not's" which may be equally worthwhile jotting down as practices to be avoided. I won't attempt to define "success." I do not necessarily mean academic recognition; I do not necessarily mean self-satisfaction; I just mean success.

First let me insert a short digression on what is meant by "clinical investigation." I recently had the pleasure of sitting in on a discussion in which our editor-in-chief, Dr. James L. Gamble, deplored the term "sub-clinical" used in the sense of "pre-symptomatic"; Dr. Chester S. Keefer, who was present, enlarged on this theme and pointed out that "clinical" is derived from the Greek word "klinikos" meaning bed, and that "sub-clinical" (a Latin-Greek hybrid) literally means "under-the-bed." Since animals do not sleep in beds it is quite clear that "clinical investigation" has primarily to do with the investigation of sick people, and is concerned only secondarily, if at all, with sick laboratory animals. But more of that in a minute.

I think of a clinical investigator as one trying to ride two horses,—attempting to be an investigator and a clinician at one and the same time. Whereas such an equestrian manoeuver is usually considered a bad policy, in this case, probably because of two considerations in particular, experience has shown that it is a very fruitful pastime. In the first place, the ultimate goal of most investigation is to find something of benefit to the human race; where, other than by the bedside of sick patients, could one find so many suggestions of things to be investigated? Secondly, in many instances, nature has arranged an experiment in a sick individual and partly completed it; all that is needed are the eyes of the clinician to make certain observations, and the background of the investigator to plan other observations and interpret them.

This rider of two horses, however, must remember that there are two horses; he must avoid the danger on one side that he, as a clinician, be swamped with patients and the equal danger on the other side that he, as an investigator, be segregated entirely from the bedside. In his laboratory, necessarily easily accessible to the wards, his clinical half will be constantly interrupted by such messages as that Mr. Humpty-Dumpty has had a big fall. As a result, his investigative half will find that he cannot compete with the straight non-clinical investigators as regards animal or smoked-drum experiments. To answer a vital question, where such technics are necessary, it is often preferable that he persuade one of his non-clinical colleagues to carry out the observations. You can all look around you and see many examples where a good clinician has gone to the laboratory to get the answer to a question and has gotten it,—more power to him. All I am trying to say is that, if you have acquired the difficult technic of being a fair clinician, you had better use this technic in your clinical investigation.

Let me add one additional point: an intelligent patient, private or otherwise, to whom you have taken the trouble to explain the nature of the investigation, makes the best laboratory animal.

I would not feel quite right addressing this Society without presenting one of what Dr. James H. Means has termed, because of the arrows, my St. Sebastian diagrams. Accordingly, I have arranged one such (Figure 1), depicting the "Do's" and the "Do-not's" which one must pass by in climbing the road which leads to the Castle of Success in Clinical Investigation. You will note that the road is formed by the amalgamation of two paths,

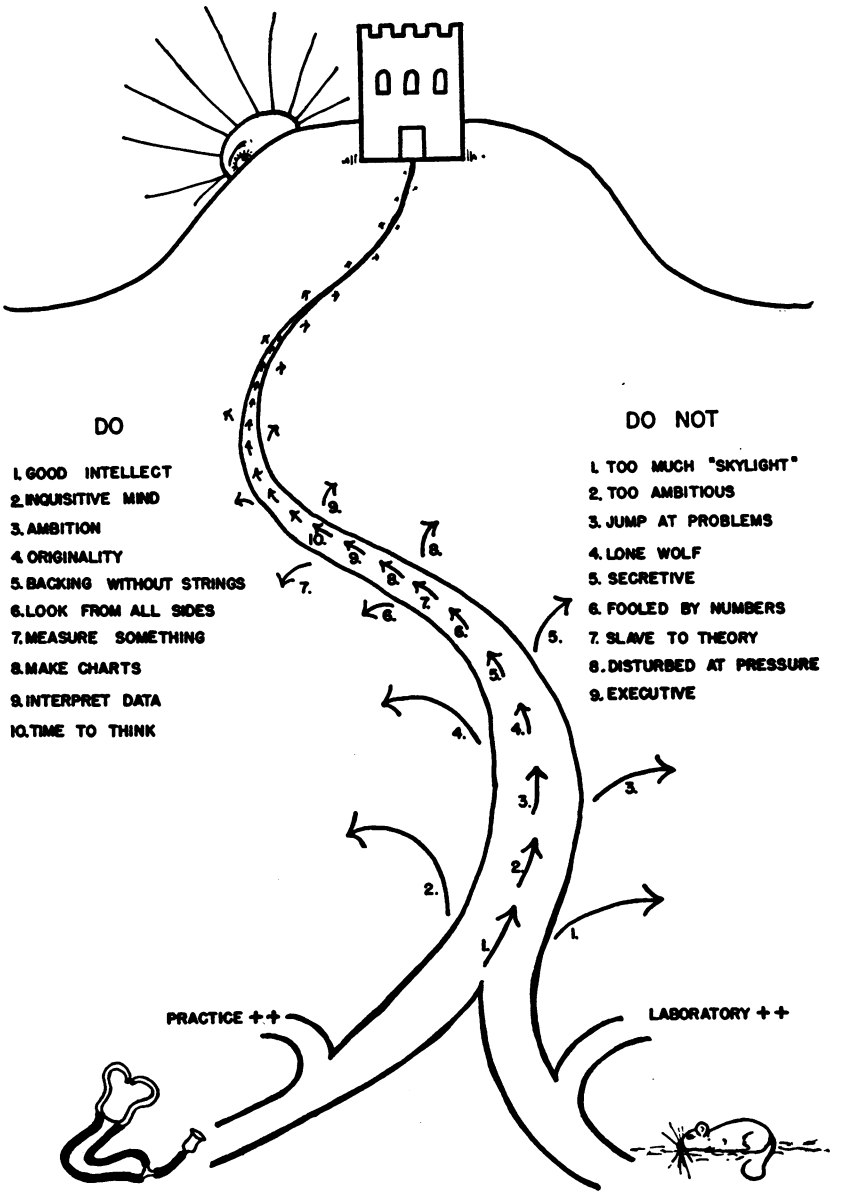

FIG. 1. THE "DO'S" AND "DO-NOTS" ALONG THE ROAD LEADING TO THE CASTLE OF SUCCESS IN CLINICAL INVESTIGATION.

one representing the clinical side and the other the laboratory side.

"Do" No. 1. Do be born with a good intellect, not necessarily the best of intellects. Oliver Wendell Holmes divided minds into "one-story intellects, two-story intellects, and three-story intellects with skylights." "All fact-collectors," he noted, "who have no aims beyond their facts, are one-story men. Two-story men compare, reason, generalize, using the labors of fact-collectors as well as their own. Three-story men idealize, imagine, predict; their best illumination comes from above through the skylight." One sees the same types among clinical investigators; all three have their places. We all know the data collectors, who fill the literature with amorphous data but do not tell us what the data mean. We can look around us, too, and see a few three-story intellects with skylights. One such was the late Dr. L. J. Henderson. It is often unnecessary for the highest intellects to do any collecting of data; they can often take somebody else's published data and arrive at some important new truth. This requires no laboratory animals, no complicated chemical determinations. In this connection,

Dr. Read Ellsworth once cited an excellent example. Throughout nearly an entire lifetime, Tycho Brahe sat in his laboratory assiduously observing and recording, night after night, the precise position of the planets and stars. Kepler, a calculator par excellence, seized upon this amorphous mass of figures and out of the confusion there emerged three great laws of the movement of the planets. This fortuitous combination of Tycho Brahe's patient accuracy with Kepler's ability to reason and calculate, the one-story intellect with the three—, turned out to be extremely significant for Science.

"Do-not" No. 1. But, do not have your skylights too widely open; install some venetian blinds. There is a real danger in having more mind than matter, as Dr. E. Cowles Andrus aptly put it,—of having so many ideas that one flits from problem to problem without ever completing anything. After perhaps ten years of flitting, our intellectual genius wakes up to find that a one-story intellect friend, who has had but one thought, has proved it beyond all manner of doubt while he himself has had innumerable brilliant theories all of which still remain theories.

"Do" No. 2. Do develop an inquisitive mind. Some people can look at a problem and never see that there is a problem; in the words of the late Professor Jacob Erdheim, with whom I spent a very profitable year, "Die Augen sind gut, aber sie schauen nicht an." Professor Erdheim was constantly asking himself, and surprisingly often answering the question: "Wass is die Ursache?" If you don't ask the questions, you won't find the answers. For example, most doctors would look at a patient with Paget's disease with bowing in one leg and not the other and would fail to ask themselves why the bowed leg is long enough to reach the ground,—in fact is as long if not longer than the other leg. If one asks the question, as did Professor Schmorl of Dresden, and looks for the answer, the explanation is simple and quite interesting (1).

"Do" No. 3. Do be ambitious. Ambition breeds energy. Clinical investigation requires sweat, if not blood and tears!

"Do-not" No. 2. Do not be too ambitious. Too-much-ambition breeds jealousy; jealousy breeds unhappiness. At any one time, credit seldom goes where credit is due. When the partition of credit leaves our over-ambitious colleague on the short end, he boils. Let our unhappy colleague whose work has produced important negative evidence keep his sense of humor; his more discerning colleagues recognize that, in the labyrinth of Science, to point out that one door after another is not the right one is of great help to those who follow. With many intricate problems, it is necessary first to demonstrate that two and two do not make five or six or seven, before the fellow who gets all the credit comes along and discovers that they make four. In short, let our colleague remember that, in the long run, credit does go where credit is due.

"Do" No. 4. Do have that something which, for want of a better term, I will designate "originality." One can possess the best of intellects and still fall down in investigation because one is completely lacking in this. I do not think that the prospective investigator, or his adviser, can tell without his actually trying whether this important but intangible quality is present. I am not sure that one cannot acquire it. I rather think that a well-developed ability to correlate ideas may almost take the place of what I am talking about.

If one makes it a practice every time one hears of a new and interesting fact to ask himself if this fact has any bearing at all on his own particular pet problem, it is surprising to find how often it may have. For example, one hears that phosphatase is found in the kidneys. The parathyroidologist asks himself: "Does this have anything to do with parathyroid function?" "Well," he muses, "the parathyroids have something to do with excretion of phosphates in the urine. Phosphatase has something to do with getting phosphates across membranes. Ergo, does the parathyroid hormone influence the amount of phosphatase in the kidneys?" [1] The final question may have the appearance of an original thought when as a matter of fact it is the logical outcome of a process of correlation,—of putting a few known facts in juxtaposition as it were.

"Do" No. 5. Do obtain a backing, financial and otherwise (Don't ask me where!), which leaves you absolutely free to pursue whatever project seems most promising. The man and not the project should be endowed. His natural interest may take him from calcium to parathyroids, to bone disease, to kidney stones, to urinary infections; from calcium to bone disease, to gonadal hormones, to ovarian dysfunction, to amenorrhea, to hypothalamus, to psychosomatic medicine, etc., etc. Too often promising work in one field is interrupted because somebody with a bank account wants to know the answer to some specific problem such as the cure for cancer, the cause of otosclerosis, or what have you. New knowledge, be it where it may, is of importance, and the cure for cancer may come from somebody who is working in a field apparently entirely unrelated to cancer. I am told that the Russians are encouraging scientific research of any kind. Certainly from the 1940–41 programs of the Biochemical Society of London one would never suspect that England was in a life-or-death struggle.

"Do" No. 6. Do look at your problem from all points of view; don't get too close to it at first, but cover the entire field with a low-power lens; then when some point of interest presents itself turn down on that with a high-power lens.

Most problems in clinical medicine are best approached from several directions. Take the subject of hyperparathyroidism. The clinical side tells us that some cases have such and such symptoms in relation to their skele-

[1] This series of questions was stimulated by the interesting investigations of Dr. Charles D. Kochakian of Rochester, N. Y. He went through the same process of reasoning and is now in the process of obtaining the answer to the final question.

tons, that others have no skeletal symptoms, that kidney stones and polyuria are common, whether or not skeletal symptoms are present, etc. The morbid anatomy of the bones shows us that there is a very rapid turn-over of bone tissue in those cases that have bone disease and that there is absolutely nothing abnormal going on in the bones in those cases that do not have bone disease. The chemical side tells us that the level of serum calcium is high and the level of serum phosphorus is low whether there is bone disease or not, but that the serum phosphatase level is high only in those cases with bone disease, etc. The metabolic studies tell us that the urinary calcium and phosphorus excretions are high in all cases whether they have bone disease or not, that a patient need not be in negative calcium balance if the calcium intake is sufficiently high, etc. But the combined approach, which takes in clinical aspects, morbid anatomy, chemical findings, and metabolic observations, leaves us with some idea what the disease is all about.

"Do-not" No. 3. Do not jump at the first problem which presents itself. When I first started investigation, I thought that it would be virtually impossible to find a problem which had escaped the attention of eager investigators since the beginning of time and which gave any hope of being soluble. As a matter of fact, there are good problems everywhere. Remember, it is much easier to start an experiment than it is to finish one. This is one lesson that I have never been able to learn; I hate to think of the grief I would have been spared had I learned to count ten before launching into a new problem.

There are certain reservations, however, which should be made to the above. In clinical investigation it is often necessary to start a new problem on the spur of the moment in order to employ some unusual opportunity produced by disease. A reverse reservation is that certain problems should never have been started. And here it should be sadly but firmly recognized that it is a mistake to go on and on in the hope of salvaging something rather than to scrap the whole wretched business.

"Do-not" No. 4. Do not be a lone-wolf investigator, —one who never discusses his results or methods of approach with anybody else, who never invites criticism. Most problems are sufficiently complex that they require for their solution the combined efforts of a group. This group need not necessarily be set up as a group under one chief; one investigator working by himself in his own laboratory is not a lone-wolf investigator if he frequently seeks the advice and help of his colleagues in other laboratories—if he makes it a practice to attend the "May meetings" in Atlantic City, and puts in some good work comparing notes on the boardwalk.

"Do-not" No. 5. Do not be secretive. Talk about your work without fear that somebody will publish before you. The danger one runs of having intellectual property pirated is far offset by the suggestions one receives from colleagues. I recall waiting for the report of certain experiments, the details of which were kept secret; when the report finally came out it was full of loopholes which might have been eradicated had the authors discussed their findings with others. I am quite sure that nine times out of ten, when an investigator believes that his work has been pirated, this is not the case. Knowledge accrues usually in a logical manner. The next step comes when the stage has been set. It is not surprising when two or three laboratories arrive at the same answer at the same time. Material which is rushed into print for the sake of priority is usually from the hands of one-story intellects, trying to beat other one-story intellects in reporting some perfectly obvious experiment.

Furthermore, half the fun of investigation is talking about it. If one talks only about the experiments one has completed and proved, one will have relatively little conversation; if one talks about all the theories one has not yet proved, the sky's the limit.

"Do" No. 7. Do measure something. I need not remind you gentlemen that science is based on measurements. Indeed this is so well-understood today that at times one wonders whether the pendulum has not swung too far from the state of affairs in the Middle Ages. Then it was all metaphysics and no measurements; now it is all measurements and no metaphysics. Perhaps a dash of the latter would be a useful condiment.

The real problem is what things to measure, how to measure them, and especially what control measurements to make. I have no special thoughts on this subject other than one minor point. In general, one should make the measurements to answer the problem; not look for a problem which will be an excuse for carrying out certain complex measurements. This assertion must of course be qualified. An interesting new investigative tool is discovered (e.g., isotopes); it is certainly intelligent to do a bit of prospecting with this new tool in order to determine where in the investigative field it will produce additional information. Some investigators are born gadgeteers; they love complicated set-ups. Some of the best advances, however, have been made with very simple measurements. The determination of the weight of hair produced in an axilla, expressed in grams per axilla per week, may give you the same information, mirabile dictu, as an assay of the urinary excretion of that steroid which has a ketone group on the seventeenth carbon atom.

"Do-not" No. 6. Do not be fooled by figures. Granted that figures do not lie and that liars figure, the fact remains that figures can give you a false sense of security. One can prove statistically that one set of figures is significantly different from another set; the question remains as to why they are different. No matter how careful you are, in almost any experiment another variable than the one you are studying creeps in and may be the cause of the changes observed. In studies on calcium metabolism, for example, the unaccounted for variable may be the amount of ultraviolet light in the atmosphere or the amount of calcium swallowed with the tooth powder.

"Do" No. 8. Do where possible arrange your data in chart form. This has long been a recognized practice with certain variables,—especially temperature, pulse, and respiration. The importance of charting was first brought home to me at Johns Hopkins where Dr. Warfield T.

Longcope has his students chart any variable that can be charted. I remember particularly a case of undulant fever with intermittent hydrarthrosis where Dr. Benjamin M. Baker, Jr. charted the circumference of each knee and found that the right knee was swollen when the left knee was down and *vice versa* in perfectly regular 7-day cycles (2). These are very interesting observations which probably would never have been made had the data been entered in the record as so many separate notations. Incidentally, these observations of Dr. Baker have been in the literature now for 15 years. It is about time some inquisitive mind put forth a theory as to why one knee was swollen when the other was down and why the cycles were exactly 7 days. I can hear Erdheim's spirit mumble: "Wass is die Ursache?"

In the preparation of data for publication, I also believe a chart is extremely helpful to the reader; it should not, however, replace tables of data, which are much more convenient for the three-story intellects who will usually wish to make some recalculations.

"Do" No. 9. Do develop a theory or, at the very least, do try to correlate your work with the sum total of human knowledge. Don't burden this weary world with data without giving a hint as to the reason why they were collected and what they mean. As some of you know, I am one of those who believe that any theory is better than none at all. For example, I am not happy with the statement that, on administration of parathyroid hormone, the serum calcium rises and the serum phosphorus falls. I want to know whether the serum calcium rises because the serum phosphorus falls or whether the serum phospohrus falls because the serum calcium rises, and what is more, I do not want the authors to straddle the issue.

The purpose of a theory is twofold: (*a*) to give you something upon which you can hang the facts, and (*b*) to give yourself and your colleagues something to tear down and replace with a better version. By "theory," you will note, I really mean "working hypothesis."

"Do-not" No. 7. Do not be a slave to your theory. When new facts present themselves which require a change in the theory, change the theory. Do not feel hurt if somebody else changes it for you. Do feel hurt if your facts are wrong; not if your theories are wrong.

"Do-not" No. 8. Do not be too disturbed at pressure exerted upon you to produce tangible results, *i. e.*, papers or reports. Often one hears lamentations over the "constant pressure to produce something." Such pressure has its obvious faults, but may be a blessing in disguise. Often, there is a certain amount of inertia about actually working up one's data and yet, not infrequently one's best thoughts do not come until one attempts to put down one's findings in black and white. Alas, it is too often only then that one really finds the shortcomings of one's data! Furthermore, if one waits a period of years with the expectation of getting out a magnus opus when the work is completed, one should remember that worthwhile work is seldom completed. There is always just one more answer which the inquiring mind would like to have. Finally, the data become so voluminous that the mind shrinks from assembling them.

"Do-not" No. 9. See to it that you do not wake up some fine morning in an executive job. Do not show too much administrative ability. The first time you are asked to serve on a committee, be anything but efficient. Never make the mistake of proposing some new reform; you are apt to be chosen as a committee of one to put said reform through. The desk of the good executive should be clear; that of an investigator should be littered. Questions will constantly come up which cannot be immediately settled and filed away. They must be pondered over. Whatever else you do, do not become a Professor of Medicine or the head of a department. Let me make it clear that I do not deprecate the good executive. I realize that it may be commendable for a man to sacrifice his own investigative career to direct the investigations of others. He may climb to bigger and better castles but his chances of arriving at the castle under discussion lessen with his executive duties. I appreciate too that some men manage to continue their investigative work in spite of the fact that they become executives. I am cognizant that the top academic jobs are mostly executive and must be filled by the top academic men. I am aware of the fallacy of the often-made suggestion that the administrative jobs be filled by men with executive and not necessarily academic ability. I have little constructive criticism to offer at this point. An obvious suggestion is to find some Lady Bountiful to endow some purely research associate professorships in clinical departments. But I am not sure that this would work; there is such a thing as being too sheltered from the world of responsibility. Certainly such professorships should not be relieved of the responsibility and stimulation of teaching and care of patients.

There is another more subtle way to find oneself eased into an executive job. You start, shall we say, as a young investigator apprenticed to a seasoned veteran; perhaps a small corner of the laboratory is allotted to you where you can carry out your measurements. The first step forward comes perhaps when you get sufficient money from some fund to hire a technician. Then your work may attract the attention of some bright young investigator who attaches himself to you; then come more funds, more technicians, and more assistants. All the financial grants require yearly reports; data are collected which have to be gone over; papers have to be written; speeches have to be made; teaching has to be taught; pretty soon one is less and less in the laboratory and more and more at his desk. You are caught—the fun of directly carrying on investigation is not for you;—you are an executive.

"Do" No. 10. Do try to reserve some time during the day when you can do some unadulterated thinking. If you salvage a few minutes, you will be doing better than most. Some people, the peripatetic school, do their thinking while walking around; they bump into you in the corridors and get the reputation of being absent-minded. Some think while they are driving their auto-

mobiles; this has its disadvantages to the public at large. Some get a few minutes while walking to and from their work; this is excellent. But most seize a few relaxed moments while taking the morning hot shower; this may lead to a hot water shortage if some particularly difficult concept has to be thought through. Let thinking come where it will, the important thing is that time be found to put the new facts which have come before one's sensorium in juxtaposition to the old problems.

LAST LAP

Well, you do the "Do's" and you do not do the "Do-Not's"; you arrive at the door of the Castle of Success. You still need the key to open the door. The key stands for the personal equation. "But personality does not count in pure science," you say. That may be true, but Clinical Investigation is not a pure science.

BIBLIOGRAPHY

1. Reifenstein, E. C., Jr., and Albright, F., Paget's disease: a concept as to its pathologic physiology, and the importance of this in the complications arising from fracture and immobilization. New England J. Med. (in press).
2. Baker, B. M., Jr., Undulant fever presenting the clinical syndrome of intermittent hydrathrosis. Arch. Int. Med., 1929, 44, 128.

The Mechanism of Pyridoxine-Deficiency Anemia. By GEORGE CARTWRIGHT (by invitation) and MAXWELL M. WINTROBE, Salt Lake City, Utah.

Pyridoxine deficiency has been studied in swine with special reference to the anemia and its relationship to protein metabolism. The anemia is microcytic and hypochromic in type and is accompanied by an elevated serum iron, hemosiderosis of the tissues, and bone marrow hyperplasia. Nevertheless studies on serum bilirubin, reticulocytes, icteric index, and urobilinogen excretion showed that there is no increase of blood destruction. The anemia appears to be due to faulty synthesis of hemoglobin. The ferremia and hemosiderosis are prevented by restricting the dietary intake of iron. This indicates that the hemosiderosis is caused by the continued retention of iron at a time when its utilization for hemoglobin formation is at a minimum.

The place in hemoglobin formation at which pyridoxine exerts its action was sought by feeding a variety of substances, including chlorophyll, and hemin, to pyridoxine-deficient animals. The metabolism of tryptophane is disturbed in pyridoxine deficiency and three products of tryptophane metabolism are found in increased quantities in the urine of deficient animals. The significance of the finding of certain urinary pigments in cases of nutritional deficiency is discussed in relation to these observations and the factors concerned in hemoglobin formation are considered.

Panmyeloid Arrest in Rats Produced by a Purified Diet Containing Sulfaguanidine and Corrected by Liver or Yeast Extracts.[1] By FRANK H. BETHELL and (by invitation) MARION E. SWENDSEID, and RAY H. ROSENMAN, Ann Arbor, Mich.

Young mature rats maintained on a vitamin-free diet containing 2 per cent sulfaguanidine and supplemented by crystalline vitamins develop progressive leukopenia, granulocytopenia, thrombocytopenia, and normocytic anemia. It has been shown that these changes are the apparent result of a conditioned nutritional deficiency induced by the bacteriostatic effect in the intestine of the sulfanilamide derivative. The lowered values may be prevented or corrected by extracts of liver or yeast containing "folic" acid (vitamin B_c).

At the maximum observed developmental arrest, the marrow total nucleated cell count is but slightly less than that of normal rats. However, the majority of the marrow cells in the affected animals are undifferentiated primitive forms, with relative increases in myeloblasts and early erythroblasts. Myelocytes, late erythroblasts, and megakaryocytes practically disappear.

By means of marrow differential counts, performed on successive days after the administration of such liver or yeast extracts, it has been possible to determine the change in relative numbers of cells at each stage of development of the granulocyte and erythrocyte series. A close parallelism in the maturation of the members of the two cellular series is demonstrated. These observations provide evidence in support of the theory of a common stem cell origin of all blood cells developing in the marrow of the rat.

Studies on Increased Coagulability of the Blood. By THEO. R. WAUGH and D. W. RUDDICK (introduced by Donald McEachern), Montreal, Canada.

The need for a test to demonstrate the presence of an increased coagulability of the blood has been accentuated by the recent interest in thrombosis and the use of dicoumarol.

Such a test using heparin as an anticoagulant is here presented. By thus slowing the process, finer analysis of any abnormalities, particularly acceleration, is made possible.

The result is expressed as a graph and experimental evidence along with the theoretical consideration of the mode of action of heparin indicates that this method may be a measure of the relative thromboplastic content of the blood.

Studies employing this test demonstrate a small range of variability in normal individuals and an increased coagulability, (*1*) during uncomplicated bed-rest, (*2*) following operative procedures, and (*3*) in the presence of acute infections.

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[1] The liver extract was supplied by the Wilson Laboratories. The yeast extract was supplied by Parke, Davis and Company and contained 85 gammas of vitamin B_c per ml.