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University of Minnesota Medical Bulletin

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Medical Bulletin

OFFICIAL PUBLICATION OF THE UNIVERSITY OF MINNESOTA HOSPITALS, MINNESOTA MEDICAL FOUNDATION, AND MINNESOTA MEDICAL ALUMNI ASSOCIATION

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Staff Meeting Report

Herniated Cervical Disks*

Howard C. Chandler, M.D.,[1]
Bo Sung Sim, M.D.,[2] Lyle A. French, M.D., Ph.D.,[3]
and William T. Peyton, M.D., Ph.D.[4]

An important cause of pain in the shoulder and arm is protrusion of intervertebral disks. In the commonest form, the cervical disk syndrome arises from a small loose fragment displaced laterally and encroaching on a nerve root but not on the spinal cord. Symptoms may be relieved by surgical removal of the free part, especially if redundant bone is scant.

When the cord is compressed by hypertrophic spondylosis, section of adjoining dentate ligaments is frequently helpful.

Both conditions were represented by 40 neurosurgical patients seen at the University of Minnesota Hospitals in the past five years.

Relation Between Disks and Spondylosis

Herniated cervical disk and hypertrophic spondylosis are intimately related and should be considered together. Symptoms may be identical, and the disorders often coexist.

Evidence is ample that disk lesions precede many of the hypertrophic changes in bone. Normally, the intact semifluid mass of the disk spreads the shocks and strains of everyday life over the entire adjacent surfaces of the vertebral bodies. With loss of disk content, the brunt of spinal movement falls on the outer ring, and neighboring bone becomes lipped or spurred.

In many cases, disk substance is gradually dehydrated, substance is lost, and mechanical function is destroyed in a lifelong degenerative process. Resultant thining and numerous spurs are often seen on radiograms of old people, but diffuse hypertrophic changes are rarely symptomatic, since bony ridges and projections are seldom large enough to interfere with nerves.

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*This is an abstract of a report given at the Staff meeting of the University of Minnesota Hospitals on February 10, 1956. A copy of the complete report, including tables and references, may be obtained by writing to the Editor, UNIVERSITY OF MINNESOTA MEDICAL BULLETIN, 1342 Mayo Memorial, Minneapolis 14, Minnesota.

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When loose fragments are extruded, however, calcified protuberances often play a part. A hard, unyielding ridge frequently borders the affected interspace and, though secondary, may further compress a nerve root or even cause more disability than the errant piece of disk.

In patients with longstanding symptoms, a calcified excrescence is not always removable and may continue to constrict the nerve root after a disk fragment is withdrawn.

Cervical Disk Syndrome

All herniations are probably due to basic insecurity of the disk plus trauma occurring either as a single episode or as several minor injuries. The syndrome tends to affect younger age groups than does spondylosis, particularly men, and develops mostly on the left.

A typical sharp unilateral pain usually starts in the shoulder and radiates down the outside of the arm. The hand seldom hurts but may be tingling or numb. With straining, coughing, or sneezing, pain becomes lancinating. In addition, the neck and shoulder may ache more or less constantly, and pain is often referred to the chest or interscapular region.

Mechanical defensive signs are tightness and soreness of posterior neck muscles, tenderness over the lower cervical spine, and occasional head tilting. A useful sign of rootlet irritation is production or exacerbation of symptoms by a downward push on the top of the head.

The level of herniation is often shown by neurologic signs in the involved arm. At C4 to C5, pressure on the fifth cervical nerve root generally causes deltoid weakness with sensory effects over the lateral surfaces of the shoulder and upper arm. C5 to C6 impingement on the sixth root produces biceps atrophy with hypesthesia and hypalgesia on the radial side of the forearm, thumb, and index finger. At C6 to C7, seventh nerve involvement diminishes triceps power, with sensory change over the index and middle fingers and back of the hand. The sixth and seventh cervical roots are most frequently concerned; lesions at other levels are rare.

Differential Diagnosis

Hypertrophic spondylosis as a major cause of symptoms is diffuse and noted chiefly among old people. In myelograms, several interspaces show prominent ladderlike posterior borders. A discrete portion of disk, on the contrary, is indicated by an isolated unilateral filling defect and arthritic changes may be lacking or seen only in one or two vertebrae.

Other conditions evoking pain in the upper extremity are the

scalenus anticus syndrome, cervical rib, laminar fracture, bursitis, Pancoast tumor, gallbladder disease, arthritis of the shoulder joint, and spinal cord tumor. Most of these conditions can be excluded by a careful review of the course, physical examination, radiography, and other suitable procedures.

Analysis of 40 Patients

The ordinary syndrome of radicular pain was seen in 30 subjects; the remaining 10 had signs of cord compression by midline disk hernia or calcified ridges. Many had received traction, heat, and massage without benefit.

Group 1 consisted of 26 men and four women, with an average age of 35 years. Symptoms often began within a few days after injury, generally by falls or lifting of heavy weights. The left side was usually involved. In two patients with bilateral symptoms, the stray bit of disk was placed more medially and a bony ridge crossed the midline.

All subjects had pain in the shoulder and generally in the arm and neck, often with numbness and tingling of hands and fingers. The majority had reflex changes and tender cervical spines. All but six had roentgen abnormalities of the spine, most often a narrow interspace at the hernial site. Local hypertrophy was seen in 10 and generalized overgrowth in five.

Myelography proved dependable. In 23 instances, a lateral filling defect appeared at an interspace. In 21 of these, a portion of disk was found at the same level; the other two lesions were, respectively, a large bony spur and part of a disk on the opposite side of the symptoms, The other seven myelograms revealed only moderate transverse ridges low in the neck, but in six cases portions of disks or hypertrophic spurs were later discovered.

When typical reflex and sensory changes were incomplete or mixed, reflexes were the most reliable signs of anatomic level. For example, only four of eight subjects with C5 to C6 protrusions had altered sensations in the thumb and index finger, but six had reduced biceps reflexes.

The presumed site of nerve root compression was explored by partial hemilaminectomy. At C5 to C6 level, six lesions involved a herniated fragment, and two only a bony spur. Of 19 lesions at C6 to C7, all included loose pieces of disk, and five also had sizable spurs. Remaining cases were due to part of a disk at C4 to C5, bony spurs at C5 to C6 and C6 to C7, and no apparent factor at all.

Group 2 consisted of six men and four women averaging 57 years of age. Other than severe falls in four instances, no injury was mentioned.

Chronic compression of the cord was manifested mainly by numbness, stiffness, and spastic weakness of the legs. Upper motor neurone damage was verified by abnormal reflexes. Objective sensory changes in the lower extremities were not prevalent, but two persons had slight hypalgesia and hypesthesia of the trunk and legs.

The arms were affected by numbness, tingling, flaccid weakness, decreased reflexes, or sensory loss. In addition, six subjects experienced pain in the neck, shoulders, arms, or thighs.

Roentgenograms of the cervical spine disclosed extensive hypertrophy at several interspaces, with two old fractures, and frequently one or more narrowed interspaces and marginal outgrowth.

The salient feature of myelography was transverse ridges indenting the oil column. In most instances, an exceptionally large projection constricted the cord, at times delaying flow of the radiopaque medium.

Total laminectomy was done, and the dura was opened. In six patients, the cord was squeezed by one or more massive anterior ledges in the spinal canal. The binding dentate ligaments were cut to allow the cord to shift back, away from pressure.

A large midline herniated disk was found in two patients, and as much calcified material as possible was removed. In the remaining two subjects, medium-sized ridges were observed without definite pressure on the cord, but dentate ligaments were sectioned, regardless.

Results of Operation

Most of the patients were observed four months to five years postoperatively, usually at least a year.

In group 1, a cerebrovascular death occurred two days after operation and was considered surgical. Results were considered excellent in 17, or 63%, of the 27 cases reviewed, since all symptoms disappeared. Outcome was good in six, or 22%, with only occasional discomfort.

In the 17 patients with excellent results, a detached portion of disk and practically no hypertrophic material had been found at operation. Less satisfactory results were generally related to a calcified excrescence that could not be removed.

Reflex changes and muscle weakness persisted in about half of

patients. Atrophy remained in all but one person, but objective sensory change persisted in only 10%.

In group 2, symptoms vanished in one patient but slight spasticity and discomfort continued in four. Progression of symptoms was arrested after neurosurgery in one patient and not stopped in four.

Operations on large midline disks and surrounding calcifications produced excellent or good results. After section of dentate ligaments to relieve compression by hypertrophic ridges, two verdicts were good, one fair, and three poor. Of the two patients with no obvious pressure on the cord, one had a good outcome and the other a poor result.

Staff Meeting Report

Obesity, Body Build, and Coronary Heart Disease*

Josef Brozek, Ph.D.,[1] and Ancel Keys, Ph.D.[2]

Like emaciation and tuberculosis fifty years ago, obesity and heart disorders are now linked in the popular mind. There is much talk of reducing body weight to prevent coronary disease, our major cause of death. To the insurance industry, weight control seems the only practical approach to decreasing the burden of degenerative diseases of middle and later life.

Caloric intake is readily manipulated, at least theoretically, and the relation between weight and degenerative cardiac lesions is a promising field of research. But obesity must be differentiated from gross overweight, and body form considered in more detail. Agreed that excessive fat is generally bad, how far is it truly responsible for the coronary problem?

Rogers was the first to report, in 1901, that corpulent men were poor risks for American insurance companies. Since that time, the main evidence against obesity has come from actuarial sources. Analysis of mortality led to general adoption of higher premiums for persons much above average weight for height and age. The penalty usually begins with a surplus of 20 to 22%, or about 30 to 35 pounds, and increases proportionately.

Modern figures on overweight and high cardiac mortality are drawn largely from the extra-premium class, compared with so-called standard risks. At least for the first dozen years or so after the policy is issued, the heavy group has about 50% higher total death rate.

Mortality is up in many categories, including cardiovascular disease. Whether the coronary level is disproportionately high is unknown, a point commonly ignored. The latest insurance publication mentions lack of a good basis for rigorous comparison.

Obesity, Overweight, and Body Build

We must look to definitions. Obese means overfat, yet insurance

*This is an abstract of a report given at the Staff meeting of the University of Minnesota Hospitals on February 17, 1956. A copy of the complete report, including tables and references, may be obtained by writing to the Editor, UNIVERSITY OF MINNESOTA MEDICAL BULLETIN, 1342 Mayo Memorial, Minneapolis 14, Minnesota.

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data refer to body weight. Are overweight and obesity the same? Members of the Minnesota football team are nearly all far heavier than insurance standards but certainly not fat; conversely, some fat people have normal weight. Well developed muscles are the metabolic opposite of superfluous fat, and if coronary heart disease is metabolic, such variables must be distinguished.

Man's physique has three main aspects: (1) body size in terms of weight or volume, (2) body composition, and (3) body form, resulting from skeletal proportions and distribution of soft tissues. The Laboratory of Physiological Hygiene is concerned with means of determining composition of the human body. These are applied to problems of nutrition, aging, cardiovascular function, effects of physical activity, and the like. Methods of this type distinguish between *weight*, as judged by standards for sex, age, and skeletal frame, and relative *obesity*, defined by fat content of the body.

Among subjects with similar genetic background, age, and physical activity, relative weight and fat content are well correlated. Where groups are not homogeneous, for example, in regard to activity, relative weight no longer indicates fatness. Heavy steelworkers, like athletes, may be thin in regard to subcutaneous or total fat. The fact remains that most evidence on body build and coronary disease is limited to simple weight values.

Burden of Degenerative Heart Disease

According to vital statistics and insurance tables, cardiovascular diseases account for over half of all deaths in the United States. Malignant neoplasms contribute about a fifth, while tuberculosis and pneumonia, once among the leaders, cause 1 and 2% of the deaths.

Of the cardiovascular fatalities, more than half are due to degenerative lesions including arteriosclerosis but not hypertension. Other countries differ. Here, coronary deaths are more than four times as frequent among middle-aged men than in Italy, although non-degenerative cardiac mortality is much the same. The Bantu have extremely low rates of severe atherosclerosis and coronary disease, and in Japan, too, atheroma is very infrequent.

Necropsies

Postmortem evidence on obesity and coronary disease is anything but clear. In 1934, Rosenthal reported no association. In 1947, Wilens found severe atherosclerosis more common in fat than in emaciated people, an idea supported by Lobert in 1953. In 1949, however, Faber and Lund, using chemical methods of determining atheroma, reported findings which disagreed with those of Wilens.

Investigators in Finland and the Netherlands stated in 1947 and 1953 that the incidence of severe atherosclerosis of coronary vessels and infarcts fell sharply in the years of war, when intake of calories (and fat) was reduced.

Postmortem figures prove that atherosclerosis and coronary disease are not restricted to the obese, but it appears that atherosclerosis may be reversed by altered diet.

Overweight and Heart Disease Reviewed

On the whole, insurance companies note higher mortality and charge special premiums in the heavy class. This very factor, however, makes random sampling of the overweight improbable and tends to select poorer risks among them.

Substandard risks accepted by the Metropolitan Life Insurance Company from 1925 to 1934 have been traced to 1950 by Dublin and Marks. The effects on ultimate mortality of high weight at the time of application differed greatly in various types of disease. Total mortality in the heavy men was 150% and in the heavy women 147% of that in standard risks. Deaths from heart disease were comparable to these figures, those from cancer were the same as for standard weights, and those from diabetes nearly four times greater in the heavy group. Suicides were about three-fourths the usual rate, whatever may be said about psychologically disturbed overeaters.

Mortality among the overweight was high for all ages of policy issue, and the total for all ailments appeared larger for younger men, but not young women. Among males, life expectancy fell as excess weight increased. The female trend was less consistent, and changes with weight were smaller.

Height was a possible factor, since tall men had greater mortality, but rates were inconsistent in men of short and middle stature, and among women generally. At extremes of both height and overweight, subjects were too few for dependable statistics.

The evidence of rising mortality among overweight policy-holders is superficially convincing, yet a sharp second look might be worth while. The sample included 25,998 men and 24,901 women, with data limited to the first 12.5% of deaths. In the tabulated overweight group of both sexes, cardiovascular diseases contributed 39.8% of all deaths. How does this compare with mortality in the general population? From the information available, no precise answer can be given.

The first difficulty is that insurance data refer to a person's age at issue of the policy, but vital statistics concern population segments

in given age periods, and deaths from various causes during these intervals.

The average length of observation for the whole insurance sample was about eleven years, and age at death can be approximated. With U. S. white people for 1940 as the nearest reference point, cardiovascular deaths among overweight policy-holders were still excessive. The difference, however, was far less than when standard insurance risks were used for comparison. Cardiovascular mortality of insured heavy men was 113.2% of the U. S. rate, and of women, 104.2%.

In 1952, Levy and co-workers considered the factor of overweight among Army officers in relation to later sustained hypertension and retirement or death owing to cardiovascular-renal diseases. Men 20 pounds or more above Army standards for height and age retired at 1.5 times the usual rate. Among those who were overweight and who also had transient tachycardia and hypertension, the retirement rate was 12.3 times that in a group free of these abnormalities.

Overweight as such apparently did not significantly increase mortality, but few deaths were listed, and no special data on coronary disease were offered. Clearly, adequate surveys are badly needed as a basis for public health programs.

Weight and Coronary Disease

Among coronary patients examined in the Laboratory of Physiological Hygiene, excessive weight was no commoner than in a random sample of business and professional men of the Twin Cities. Garn and associates reported in 1951 that young men with myocardial infarction had practically the same weight distribution as healthy controls. In a large group of soldiers cited by Yater and co-workers in 1948, relative body weight associated with fatal coronary disease appeared much the same as for subjects killed by accidents. Regardless of ultimate fate, men of the same age group had similar weights on induction, and all tended to gain in service.

Wright and associates in 1954, quoting prior weights of 706 subjects with myocardial infarction, did not find that obesity favored coronary thrombosis. Nearly as many patients were below as above average weight, except at 40 to 49 years, when the heavy were considerably more numerous, and at 70 or more, when the thin group was larger.

In 1955, McVay and Keil analyzed 330 cases of myocardial infarction seen in a large southern university hospital. Both Negro and

white males tended to overweight, and women much more. No data were furnished, however, for the local healthy population, a frequent defect of hospital surveys.

Billings and others in 1949 described a doubtful preponderance of the obese among 240 subjects with infarcts. However, fat actually seemed protective, for 32% of the heavy succumbed in thirty days, 39% of those with normal weight, and 60% of the underweight.

Among several thousand Mayo Clinic patients with angina pectoris, reviewed by Block and co-workers in 1952, rate of survival was also higher among the obese – 44.4% against 35%, at best, in the non-obese after ten years. Associated diabetes allowed but 21.3% to live as long. In the total sample of 6,882, only 6.8% were considered fat.

Overweight and Blood Cholesterol

Lacking more direct information on atherosclerosis without coronary symptoms, serum cholesterol and lipoproteins are useful guides. Values are not diagnostic and apparently not prophetic for individuals, yet average values can distinguish populations with more or less coronary disease.

What, then, is the relation between overweight, obesity, and serum cholesterol? As explained by Keys and associates in 1955, the answer depends at least partly on the general level of cholesterol in the group under study. Where the cholesterol value is low, weight and obesity are related to blood content, as a rule. With high average levels no association is found, or at most, cholesterol is slightly raised in the extremely heavy class. Thus no trend was discernible in Minnesota for middle-aged presumably well men with high values around 225 mg. per 100 cc.

Diet is a factor. In southern Italy, where 20% of calories are derived from fat, mean cholesterol was 177.5 mg. In the more northern city of Bologna, with 30% of calories from fat, 209.3 mg. was recorded for a matched group. In the south, a substantial difference appeared between thinner and fatter men – averages being 151.7 and 180.8. Obesity was gauged by combined skinfold thickness at the back of the upper arm and below the right scapula.

A similar tendency was noted in South Africa. Among the Bantu, who generally have low cholesterol values, overweight individuals usually had high levels, which exceeded in the heaviest class, those of the lightest Europeans. Using arm skinfold as a more direct index of fatness, no distinct relationship was observed among Europeans.

Cholesterol increased moderately with obesity in the Cape colored group and sharply in Bantu subjects.

Effects of Weight Reduction

About 7% of the U. S. population is said to be 20% or more above standard weight. Would removing the surplus greatly lessen the burden of cardiovascular heart disease, particularly coronary disease? The reply is no.

Even if the obese person is 1.5 times as likely as the non-obese to have coronary disease, the overweight class accounts only for an excess of 3.5% of total coronary mortality. Weight reduction would still leave the adult death rate distressingly high, compared with that in some other parts of the world. Nevertheless, the effect of dietary and weight decrease on mortality, as evident in European populations during the war, deserves careful thought.

During loss of weight, serum cholesterol usually falls, only to rise with subsequent refeeding. When body weight stabilizes at higher or lower values after a change, cholesterol seems to return eventually to the level characteristic of the individual before the gain or loss.

More investigation is required. As observed in our laboratory, cholesterol mounts early in weight gain on a more ample diet and alters little when still more pounds are added.

The most widely quoted data on benefits of weight reduction are provided by Dublin and Marks. Persons rerated as standard risks after weight loss had a lower mortality rate. Since rerating amounts to a rather complex reselection, groups that have and have not reduced are not strictly comparable, however.

Special Article

The following article is reprinted, with permission of the author and the publisher, from CLINICAL RESEARCH PROCEEDINGS 3:185-187, No. 4, Nov. 1955.

Statistics, Sophistication, Sophistry and Sacred Cows

Louis Lasagna*

We are all snobs,† of course. The ego, sometimes referred to as a fragile gossamer thing, actually has an omnivorous appetite. It subsists on a diet of favorable comparisons with other egos over which it possesses a real or imagined superiority. Medical research has always provided a bounteous banquet-table for starved egos, but in recent years has begun to nourish in greater numbers persons whom I shall call Statistical Snobs.

There are two main varieties of Statistical Snobs. The first of these is the Professional Illiterate, or Statistical Hayseed. He professes a great disdain for all statistics, and boasts of his ignorance of statistical principles and technics. In ghoulish glee, he points to such books as *How to Lie with Statistics*,[1] and reminds you that "you can prove anything with statistics," or (on alternate days) that "nothing has ever been proven with statistics." He sneers at the "Ivory Tower Boys" who "just don't realize what the practice of medicine and the problems of clinical research amount to." He is shocked at the thought of controlled experiments, where some patients receive placebos and are thus "denied the benefits of treatment." (With typical largesse, this objection is levelled at all treatments, be they establishd ones of proven efficacy, or untested drugs or procedures which not infrequently turn out to be more deleterious than no treatment at all.) He is fond of writing papers (summarizing uncontrolled observations) which he admits are inconclusive, but usually end with: "The results are promising and warrant further investigation." His prevailing philosophy ranges from absolute nihilism to rapid and complete ingestion (sans mastication) of new claims, since he lacks any standard of reference for evaluation other than an ill-defined, ectoplasmic link with

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†With apologies to Russell Lynes.

the Unknown referred to as My Clinical Judgment, or My Past Experience. These individuals, while all too real, are an old phenomenon on the American scene, and actually less annoying in some respects than the second major type of Statistical Snob – the Chi Square Cavalier.

The Chi Square Cavalier, or T-test Terror, is a crusader for statistics in the scientific world. To him a paper without at least one probability value is a shuddery concept. As rigidly doctrinaire as the Statistical Hayseed, he would apply his technic to all data, even when it is not desirable or possible to do so. Since many of these Cavaliers know only enough statistics to impress those who know none at all, some rather amusing things occur at times. Data which have been collected in such a way that comparison of treatments is meaningless are subjected to exhaustive scrutiny. Matched data are treated as independent data, or vice versa. Large sample technics are applied to samples of microscopic size. A moderate amount of knowledge in this field is not, however, an impregnable bulwark against error. As a matter of fact, a special type of mistake is probably most commonly committed by a more advanced group of Chi Square Cavaliers.

The error to which I refer is the Microstatistical Mirage. Papers may be found in which "highly significant differences" are described, but which on careful reading seem to be concerned with extremely small differences which have been shown to be significant only by the use of very large samples. Several examples may help to illustrate the field of Microstatistics‡:

One paper reported the results of a study of antitussive drugs. The numeric scale for the severity of cough was from 0 to 4, as follows: 0, indicating no cough; 1, occasional, barely troublesome cough; 2, moderately troublesome cough; 3, markedly troublesome cough; and 4, incessant and distressing cough. Eleven thousand observations were made, with "highly significant" differences being established between treatments. When one looks at the figures, however, it is interesting to see that the most "potent" drug studies (codeine) caused a drop in mean severity of cough (from the 1st to the 5th days of observation) from 1.33 to 1.09, whereas the placebo caused a change from 1.58 to 1.53. Obviously the average severity of cough studied was mild, and the mean decrement after treatment small indeed.

Another paper was concerned with the calming effect of Rauwolfia on a group of agitated psychotics. Again we find large num-

‡I hope that those statisticians who refer to the statistics of small samples as microstatistics will excuse the above usage.

bers of observations made (over 400 patients were studied), with the following "highly significant" results:

	Premedication	*Placebo*	*Raudixin*	*Serpasil*
Per cent Noisy	19	19	15	14

The difference between the Rauwolfia and non-Rauwolfia conditions . . . is significant at the 1 per cent level of confidence.

Without denying the validity of small differences, one wonders whether the cause of progress is not better served in such instances by accenting the essential *insignificance* (from a practical standpoint) of such results.

The antipode of the Microstatistical Approach is presented by the Tunnel Vision (or Close-But-No-Cigar) School, members of which steadfastly refuse to call any attention to differences which do not reach some mystic probability level, no matter how close they may come to achieving this point. Even when a small series has been studied, and there is good reason to suppose that a few more cases would have allowed penetration through the Magic Wall of p. 0.05 Fire, we find the observed differences being curtly dismissed as "not significantly different." As Kennaway has recently pointed out,[2] there are very interesting examples of minute (but important) small differences which are almost impossible to demonstrate "statistically" under ordinary circumstances. He cites Haldane to the effect that the increase in length of ceratopsian dinosaurs from 1.7 to 6.5 meters in 22 million years took place (at the beginning of the period) at the rate of 1 mm. per 10,000 years. One can picture an early caveman snob telling another caveman that "All this rot about the dinosaurs getting bigger is just erroneous clinical impression, old man."

Another kind of Statistical Snob is the Placebo Pusher (or Double Blind Dodo). Having learned the magic words "placebo" and "double blind," this species insists that any report in the literature not containing these controls constitutes a complete waste of everyone's time.

If some happy clinician reports twelve cases of pathologically proven metastatic carcinoma cured within two weeks by some new drug, with maintained cure for ten years, the Dodo screams for "placebo controls." If someone reports a series of 50 cases of staphylococcal meningitis, randomly distributed to two treatment groups, with 90% survival in one and 0% in the other, the Dodo sneers, "We're the people involved in making the value judgments as to life or death kept unawares of the nature of the two medications, and did the patients know which drug they were getting?"

Like all militantly dogmatic groups, the Placebo Pushers are blissfully unaware of certain incongruities in their attitudes. For example, if one is studying the effects of nicotinic acid, injected intravenously, on headache, it is difficult to keep the injector in the dark as to which medications are nicotinic acid and which are saline, unless he is physiologically blind. (It would also help if he were deaf, so as not to hear the patients' comments.) One can get around this problem by using one person to inject and another person to evaluate the results, but how does one fool the *patient* in this case? The patient who has just got a big dose of nicotinic acid (or apomorphine, or veratrum) will usually have little difficulty in distinguishing such injections from saline.

The Placebo Pusher also has his counterpart among the nonbelievers. One recent study concerned itself with the analgesic effects of aspirin in a group of patients with chronic complaints referable to the musculoskeletal system. Having failed to show a difference between placebo and aspirin, the authors came to the astonishing conclusion that the double blind technic was not suited to the demonstration that aspirin was an analgesic drug in patients of this sort! This statement would seem equivalent to borrowing the favorite rifle of a crack marksman, missing the target, and then blaming the poor performance on the gun.

A final bit of Statistical Snobbery will be included because of its direct significance for the writer of this paper. Recently, I discussed a large series of patients who were subjected to portocaval shunts. During the early years of experience with this technic (the same surgeon did all the cases) one type of anesthesia was employed. During the later years, a second type of anesthesia became the preferred one. Since the passage of time was also associated with changes in patient selection, surgical technic, use of fresh blood, etc., I suggested that it would actually be more sophisticated for the authors to describe the results as "our experience during the first two years" and "our experience during the last two years," rather than analyze the data statistically for differences in morbidity and mortality, with an eye toward comparing the two anesthetic agents in this procedure. One critic commented that there was no point in publishing data such as these. I could hardly disagree more. Any doctor with a patient or relative with cirrhosis of the liver would be most interested to know that, as of 1955, there is a surgeon around capable of doing portocaval shunts with a very low mortality, regardless of whether he is able to put his finger on the reasons for the low mortality, and regardless of whether

he can learn from the data in the paper if ether and cyclopropane differ in their safety in this situation.

As is all too obvious, some of the descriptions above have been purposely exaggerated. These parodies are intended to emphasize certain errors which are met with all too frequently at meetings and in articles. As with most things, almost every point which has been attacked has much merit per se. In the blind or rigid application of even praiseworthy principles, however, ridiculous excesses creep in. Having been personally guilty, at one time or another, of most of the foibles satirized here, I feel considerable freedom in directing these remarks to any fellow sinners in the audience. The comments are presented not so much in the nature of stone-casting as to indicate the extreme vulnerability of the Statistical Snob to criticism by the Editorializing (or Converted Sinner) Snob.

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Editorial

Serendipity in Medicine

Serendipity is a word defined as the gift of finding valuable and agreeable things not sought for. It was coined by Sir Horace Walpole in allusion to an ancient tale "The Three Princes of Serendip" who in their travels constantly discovered by chance things they were not seeking. The word has found a place in the fact and folk-lore of medical discovery. Von Mering asked his colleague Minkowski to remove the pancreas from a dog in order to study its effect on intestinal fat absorption. According to the popular tale, a laboratory *diener* noticed that the dog's urine, excreted in large quantities, had an unusual attraction for flies. He pointed this out to Minkowski, who found the urine to be loaded with glucose. Turning aside from his main piece of work, he investigated this more thoroughly and found the dog's condition to correspond with diabetes mellitus, thus pointing to the role of the pancreas in the metabolism of glucose.

An event frequently cited as the archtype of accidental discovery was that which led to the development of penicillin. Three conditions chanced to coincide on a lucky day in 1929: a culture plate of staphylococcus, a contaminating spore of *Penicillum notatum,* and the observant eye of Sir Alexander Fleming. These and other similar occurrences are related in a delightful essay by Sir Henry H. Dale in his little volume entitled *An Autumn Gleaning.*

Experiences such as these intrigue us in retrospect. Time covers them with a patina of charm and embroiders details of questionable authenticity. They seem to be windfalls to the discoverers who made them, like the "happy thoughts" which come to gifted people without prior warning.

Sir Frederick Gowland Hopkins once said, "In a country rich in gold observant wayfarers may find nuggets on their path, but only systematic mining can provide the currency of nations."

It is unlikely that serendipity plays a predominant role in medical discovery. In contrast to penicillin, which came as H. J. L. Marriott puts it "literally out of the blue in the form of a floating spore," streptomycin and other antibiotics were found only after many years of patient research directed specifically towards the discovery of such agents. In anecdote, the stimulus of an apple's fall jarred the law of gravity from its dormancy in Newton's brain. In fact, twenty years

of careful study and calculation followed the inspiration wrought by the falling apple in the alert and receptive mind of the young Newton.

Each "accidental" discovery came to a mind alert and well prepared for it. Each discoverer was an opportunist and exploited the advantage the discovery gave him. Even the three princes of Serendip combined sagacity with the chance phenomena they observed. The "accidental" discovery appears on closer scrutiny in most cases to be not so much an accident as the co-incidence of an unusual set of circumstances and an observant, sagacious individual.

Hopkins, quoted above, though he minimized its importance, had the faculty of serendipity. According to Dale, a student in one of Hopkins' classes was unable to obtain a colour reaction for protein. Hopkins found that, indeed, with the bottle of acetic acid the student used the reaction was unobtainable, though other bottles of acetic acid gave it readily. Instead of brushing the matter aside, he investigated it further and found that the reaction was due to glyoxylic acid which contaminated most lots of acetic acid. This led him to isolate the constituent of protein which gave the reaction, tryptophane. It was the first link in a chain of discoveries by which this distinguished investigator came to a recognition of the factors we now call vitamins.

Without these little chance occurrences, it is unlikely that we would have remained very long in ignorance of the fact uncovered by them. Yet, if nothing else, they add touches of brilliance to the kaleidoscopic landscape of medical discovery.

Coming Events

March 5–7 . . . . Continuation Course in Pediatrics for General Physicians

March 6 . . . . . PHI DELTA EPSILON LECTURE; "Henoch-Schoenlein Purpura in Children"; *Dr. Katharine Dodd,* Professor and Head, Department of Pediatrics, University of Arkansas School of Medicine; Mayo Memorial Auditorium; 8:00 p.m.

March 13 . . . . . SPECIAL LECTURE; "Enzyme-Coenzyme Interaction in Flavoprotein Systems"; *Professor Hugo Theorell,* Head of Medicinska Nobel Institutet, Karolinska Institutet, Stockholm, Sweden; Room 100, Mayo Memorial; 8:00 p.m.

March 19–21 . . . Continuation Course in Cardiovascular Diseases for General Physicians

March 20 . . . . . GEORGE FAHR LECTURE; *Dr. Otto Krayer,* Professor and Head, Department of Pharmacology, Harvard Medical School; Mayo Memorial Auditorium; 8:00 p.m.

April 7 . . . . . Continuation Course in Trauma for General Physicians

April 9–11 . . . . Continuation Course in Endocrinology for General Physicians

April 16–18 . . . . Continuation Course in Radiology for General Physicians

May 7–12 . . . . . Continuation Course in Electrocardiography for General Physicians

WEEKLY CONFERENCES OF GENERAL INTEREST

Physicians Welcome

Monday, 9:00 to 10:50 A.M.	OBSTETRICS AND GYNECOLOGY Old Nursery, Station 57 University Hospitals
12:30 to 1:30 P.M.	PHYSIOLOGY- PHYSIOLOGICAL CHEMISTRY 214 Millard Hall
4:00 to 6:00 P.M.	ANESTHESIOLOGY Todd Amphitheater, University Hospitals
Tuesday, 12:30 to 1:20 P.M.	PATHOLOGY 104 Jackson Hall
Friday, 8:00 to 10:00 A.M.	NEUROLOGY Station 50, University Hospitals
9:00 to 10:00 A.M.	MEDICINE Todd Amphitheater, University Hospitals
1:30 to 2:30 P.M.	DERMATOLOGY Eustis Amphitheater, University Hospitals
Saturday, 7:45 to 9:00 A.M.	ORTHOPEDICS Powell Hall Amphitheater
9:15 to 11:30 A.M.	SURGERY Todd Amphitheater, University Hospitals

For detailed information concerning all conferences, seminars and ward rounds at University Hospitals, Ancker Hospital, Minneapolis General Hospital and the Minneapolis Veterans Administration Hospital, write to the Editor of the BULLETIN, 1342 Mayo Memorial, University of Minnesota, Minneapolis 14.