HEBERDEN ORATION, 1966*

CATEGORIZATION IN MEDICINE: A SURVEY OF STILL'S DISEASE

BY

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I must first thank you, Mr. President, and the Society, for the honour you have done me in asking me to make this Annual Oration—one of the most prized of all awards in the field of rheumatology. Essentially, what is required is a long-term view, and perhaps in this respect I qualify, since I first started to work on synovial membrane and cartilage in 1934 at the instigation of Sir Charles Dodds.

Looking at the distinguished list of my predecessors, and remembering many of the excellent orations given, I was exercised to know what I should talk about. Rheumatology, like Heberden himself in his "Commentaries" (Heberden, 1806), is concerned with the entire field of medicine, and offers a vast and almost embarrassing choice of subject. One subject I considered (but thought too difficult and left for other hands) was this problem of the development, limitations, and future of the specialty of rheumatology. During these 30 years, the field of rheumatology has progressed considerably from its spa origins, fully established even in Heberden's time and flourishing even more in the next century despite his well-expressed sceptical assessment of the value of the waters. To-day, like all other fields of medicine, rheumatology seems to be developing even faster with each returning year. In Heberden's time, the life of a vestal virgin was, he thought, no bad model for the life of a physician. "It was divided into three parts, in the first of which she learnt the duties of her profession, in the second she practised them, and in the third she taught them to others." The sacred flame must still be tended, but our time burns faster and to keep the home fires burning we have to learn as we practise as we teach, or teach as we learn as we practise, and I am sure any latter-day vestal virgins would be doing the same. I have been learning about Still's disease ever since we set up the Research Unit at Taplow in 1947 and practising and

teaching about it at the same time, with the help of a succession of brilliant colleagues and junior staff, who have asked pertinent questions and very often too have provided at least some of the answers. Like the Postgraduate School, Taplow has changed a great deal in these 20 years. It has increased in size and is much better equipped, especially since it became an M.R.C. Unit in 1958; the staff is a bit greyer in places and I hope wiser in places too, but we still have the same basic question, and most of our original patients—although we may have to chase them as far as the U.S.A. or Australia for follow-up.

The question we set out to answer now nearly 20 years ago was "What is Still's disease?" Like Heberden and his famous question "What are those little hard knobs?" (to which we still have no answer), I must talk to-day partly about the question itself and then about some of the partial answers we have arrived at, leaving it to Doctor Barbara Ansell in the Heberden Round next June to demonstrate some of the other important aspects of this entity, on which she has contributed so much.

What first of all does this question mean? It depends who asks. The patient, or here his parents, wants to know the prognosis and the proper treatment; is it a crippling disease? Can it be cured? The scientist wants to know the cause, the pathogenesis, and therefrom the possibilities both for prevention and cure. Both these different questions are dependent on a third and more basic sense of the same questions "What is Still's disease?", meaning what particular patients are said to have Still's disease and what are their common features. In fact, what are the criteria? Again, it depends what you want criteria for. No one insists on nuclear sexing when he asks a girl for a dance (although with Beatle hair-do's and clothes what they are, something like it may soon become necessary). Criteria for a population survey are different from those needed for therapeutic trials. Various sets of

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criteria have been put forward which I reviewed recently in New York at the 1966 Population Symposium. Our Taplow criteria (Ansell and Bywaters, 1959) are perhaps the simplest (Table I), requiring involvement of four joints for a minimum of 3 months; but like all criteria, we depend heavily on exclusions—so that the definition of one disease is bound up with the definition of various others.

TABLE I
CLASSIFICATION (DIAGNOSTIC) CRITERIA
USED AT TAPLOW FOR STILL'S DISEASE
(Ansell and Bywaters, 1959)

Onset before age of 16 years.
Involvement of four or more joints for a minimum period of 3 months with either pain and swelling, pain and limitation of movement, or limitation and swelling.
If fewer joints, biopsy of synovial membrane showing changes compatible with rheumatoid arthritis.
Exclusion of other diseases

Other workers have put forward more complicated criteria (Hellström, 1961, Grokoest, Snyder, and Schlaeger, 1962; Grossman, Ozoa, and Arya, 1965) again depending largely on exclusions. We have tested our criteria in a rather different way from the usual, comparing the long-term history of 25 cases meeting our criteria and followed for 10 years with the long-term history of 25 probable Still's cases—that is, not meeting our criteria—and also followed for 10 years. From Table II you will see that all except one of the definite Still's cases remained in the

TABLE II
SAMPLES OF 25 CASES OF DEFINITE STILL'S
(TAPLOW CRITERIA) AND 25 PROBABLE CASES FOLLOWED
FOR 10 YEARS

State at 10 years		Definite Still's Disease	Probable Still's Disease
Other Diagnoses	Ankylosing spondylitis	1	1
	Psoriatic arthritis	—	1
	Dermatomyositis	—	1
	Scleroderma	—	1
	Systemic lupus erythematosus	—	2
	Ulcerative colitis	—	2
	Osteochondritis	—	1
Definite Still's		←	1
Complete recovery		3	13
Remission with clinical residua		13	2
Continued activity		8	0
Radiological residua in hands, feet, or neck		16	2
Growth anomalies		10	1

“definite” category after 10 years; that one exception developed ankylosing spondylitis. Of those *not* meeting the criteria (four joints involved for at least 3 months), the “probables”, you will see that only one has become definite in those 10 years and most of the other have developed the symptoms of some other disease. None of the probables continued disease activity and the majority have made a complete recovery as compared with the definite group, so that at least our criteria do the job we want them to do—to select those who will remain in this category and to exclude those who will later develop signs and symptoms pointing to some other disease—but does what we have found relate to any real entity?

George Frederick Still (Fig. 1) was wiser than we. He gave a description but no definition. He used the term “a form of chronic joint disease in children” rather than “Still's disease” and he described the latter on the basis of twelve out of 22 cases (of which he had personally seen nineteen in a brief 2-years' residency at Great Ormond Street: Still, 1897).

Fig. 1.—George Frederick Still, after the painting by Gerald F. Kelly in King's College Hospital (Reproduced by permission).

He said there were three types:

- (i) the rarest, Jaccoud's syndrome (1 case);
- (ii) rheumatoid arthritis as in adults (6 cases);
- (iii) a special category of twelve cases characterized by glandular and splenic enlargement.

He was, you will see, a splitter rather than a lumper, and in the forefront of his time, since progress involves having four or five diseases for every one of 10 years ago, but he never returned to the subject. Now, there is some practical point in separating similar syndromes if prognosis or treatment differ or if pathogenesis is known to be different, but every patient has in one sense his own disease, and prognosis and treatment should always be individualized. If genuine "overlap" occurs commonly, if there is gradation from one syndrome to another, it is unlikely that the separation will be found to depend on basic pathogenic differences.

To return to Still's three categories. The first, Jaccoud's syndrome, we have not seen in childhood, and I think it unlikely that the one case Still described really falls into this category as we have defined it (Bywaters, 1950) based on some ten cases, the youngest of whom was 28 years old—that is, a chronic post-rheumatic fever capsular fibrosis of the small joints of the hands and feet, with fibrosis in the joint capsule, probably similar to that developing in the valve ring and with similar timing. On the other hand, we have seen a number of children with classical rheumatic fever developing chronic changes in joints, during the healing stage of their disease after the erythrocyte sedimentation rate has returned to normal, and these may closely mimic rheumatoid arthritis and go on to the type of fibrosis that Jaccoud originally described.

The second category that Still distinguished was rheumatoid arthritis as in adults. Most people agree that occasional cases of chronic polyarthritis in childhood are of this nature, even to the presence of rheumatoid factor, nodules, and vascular lesions. Vascular lesions such as we have seen in adult rheumatoid arthritis since 1946 are very rare before the age of 16. I remember only one child who showed the typical nail-edge or nail-fold lesion. At the age of 11 or 12 she developed nodules and vascular lesions and became transiently sero-positive: an arteriogram showed some blockage of digital vessels. Nodules are less rare than vascular lesions, occurring in about 8 per cent. of children meeting our criteria. While rarely they may resemble histologically those of adult rheumatoid arthritis, with palisading and central necrosis (about 1 in 10), the majority of those we have biopsied resemble much more nearly the nodules of rheumatic fever, with no palisade layer but a lot of fibrinoid lattice, as Zeldis, Glynn, and I showed in 1958, when a blind survey (if you know what I mean) put ten out of eleven biopsies into the rheumatic fever rather than the rheumatoid class (Bywaters, Glynn, and Zeldis, 1958). In fact, if

typical rheumatoid nodules with palisading occur in children (slides of which I get sent from time to time), these are the subcutaneous nodules of granuloma annulare, a benign, relatively common, and often recurrent disease (which we have seen occur by chance even in rheumatic fever or adult sero-negative rheumatoid arthritis) usually made manifest diagnostically by cutaneous nodule formation. There is a close link between nodules and sero-positivity even in Still's disease, nodules being present in seven out of 28 sero-positive patients (25 per cent.) as against only 3·5 per cent. of those who were sero-negative, the only positive correlation with serological findings. The rheumatoid factor is present, using the differential agglutination titre, in about 15 per cent. compared with a much higher proportion (about 60 per cent.) of adults, and it remains positive in this group with the passage of time; thus 14 per cent. of our group were originally positive and 10 years after the onset the same proportion are positive; although one or two have become negative and one or two negative ones have become positive over this period, the majority have stayed the same over the 10-year period. More recently, Dr. Holborow has been using the F II haemagglutinin method of demonstrating rheumatoid factor, which is more sensitive; this runs in general parallel with other methods and is positive in 30 per cent. of cases of Still's disease, as against 90 per cent. of cases of adult rheumatoid arthritis (Table III). There are still 50 per cent. of Still's cases with no F II titre at all. In general, those few with a positive DAT which resemble the rheumatoid arthritis of adults, tend to have a more severe course than those with a negative sheep

TABLE III
F.II HAEMAGGLUTININ TITRE IN 72 CASES OF ACTIVE STILL'S DISEASE COMPARED WITH DAT AND LATEX TITRES
(Holborow and Johnson, 1966)

DAT	F.II titre				
	Up to 100	200-400	800-1600	3200-6400	12800 +
16-32	1	3	1	1	3
4-8	9	9	2	3	0
1-2	37	4	5	3	0

Latex Titre	Up to 100	200-400	800-1600	3200-6400	12800 +
++	1	1	1	3	3
+	0	1	2	3	0
Negative	46	7	3	1	0

cell agglutination titre, a finding which is true also in adults. However, we have not yet made enough observations on the presence of intra-cellular rheumatoid factor in sero-negative Still's cases, which Mellors, Nowoslawski, and Korngold (1961) have demonstrated, but this is obviously an important lead to follow.

The third category of cases is one which Still himself thought to be a special type of disease and characterized by fever, lymphadenopathy, and splenomegaly. Technically, this alone should be called "Still's" disease, but we have little evidence that these characteristics are themselves specific; even in adult rheumatoid arthritis, fever occurs and lymphadenopathy and splenomegaly are not uncommon. The majority of the children with chronic polyarthritis that we have seen in the last 20 years, which now number over 400, have been sero-negative, and only comparatively few of those meeting our criteria have turned out to show other syndromes in recognizable form. We have made special efforts to follow all the children we have seen. Barbara Ansell in particular has done a wonderful job in maintaining contact and confidence. It is only by such long-term surveillance that any knowledge is to be gained, and only by such continued social and medical care that good therapeutic results can be achieved.

When we first examine children sent to us with chronic polyarthritis, some meet our criteria, some have "probable Still's" (not meeting our criteria), and others have other recognizable entities—such as psoriatic arthritis, ankylosing spondylitis, or ulcerative colitis arthritis. As we follow these patients over the years, a few in the definite Still's group may develop signs of psoriatic arthritis or ankylosing spondylitis, but the majority stay as originally categorized (Ansell and Bywaters, 1962). The "probable" group, however, tend to develop such other diseases quite frequently; only five of these have developed signs to put them in the definite group and others have developed other syndromes such as ankylosing spondylitis, rheumatic fever, Raynaud's phenomenon, systemic lupus erythematosus, scleroderma, or dermatomyositis. Even here, however, 23 of the group of 43 probables still remained in the probable group at the end of 5 years. Others, developing bouts of diarrhoea, may develop ulcerative colitis, as in a patient whose first colonic symptom started 1 year after the onset of his arthritis. Occasional backache also needs attention, and even in females may sometimes be due to ankylosing spondylitis with spinal and sacro-iliac change.

Other diseases we have also seen mimicking Still's disease include leukaemia, reticulo-sarcoma (Fig. 2), and neuroblastoma, which only later declares itself with the characteristic facial swellings.

The crux of the problem is not such misdiagnosed cases or the cases which patient follow-up allows one to classify differently, but the large majority who have just "Still's disease", or even just "probable Still's disease". It is easy to answer the question "What is rheumatoid arthritis?", if we adopt the negative position of saying it is *not* psoriatic arthritis or *not* ankylosing spondylitis or *not* this or that or the other, but in fact this is what has happened. A continuation of historical dichotomization has led to the position where we now regard the rheumatoid factor as a marker but have more sero-positive people in the population at large *without* rheumatoid arthritis than *with* it (four times more, according to Lawrence, 1963); we have a large number of sero-negative cases of rheumatoid arthritis and do not know what to make of them, and we also have many cases of Still's disease with sacro-iliac fusion but no involvement of the spine. In short, we are left to define this group of cases using the same old clinical features that Still used. We do know a great deal more about the disease and we have added a number of features that Still did not mention (such, for instance, as rash), but we still have no specific test and, perhaps now with the aid of computers, we still have to depend upon these constellations of signs. I propose now to talk about some of these special characteristics of juvenile rheumatoid arthritis.

Fever.—This is characteristically very high in the evening, returning to normal by morning, unaffected by the antibiotic frequently prescribed in the mistaken belief that it is due to infection, but controlled by salicylates in adequate dosage. In a study with McMinn (McMinn and Bywaters, 1959), we have shown that such a fever is characteristic (but by no means invariably present) and contrasts quite markedly with the typical chart of rheumatic fever, where the fever tends to swing less and to stay higher. It is sometimes seen in adults. Sometimes fever may be the presenting sign and may recur regularly year after year without much in the way of joint involvement, accompanied perhaps only by the rash.

Rash.—The typical rash of Still's disease is small and does not spread, occurring towards evening with fever, and is to be distinguished from the marginate spreading rash of rheumatic fever (Isdale and Bywaters, 1956). We have tried to see whether this rash has any specific correlations. The most marked

Fig. 2.—Right hand and x ray of an 8-year-old boy with a 3-week history of painful swollen hands with fever, responding to salicylates E.S.R. 51 mm./hr. Diagnosis—reticulo-sarcoma. Note diaphyseal and subcortical rarefaction.

Fig. 3.—Keratitis punctata in a 10-year-old girl, 7 weeks after onset of polyarthritis. E.S.R. 39 mm./hr; DAT negative. No eye symptoms.

Fig. 4.—End-result of iridocyclitis in a woman now aged 53. The onset of Still's disease had occurred when she was aged 4½ years, and iritis started when she was aged 7 years. Note calcific deposits (band opacity) and synechiae.

was with fever and to a somewhat less extent with lymphadenopathy and splenomegaly, but it was seen both in those with a positive sheep cell test and in those without. It is also rarely seen in adults, and such adults run a course somewhat like that of Still's disease, are usually sero-negative, and can, I think, be said to have "*adult Still's disease*".

Glandular Enlargement and Splenomegaly.—Of the other features which Still described in his twelve cases, glandular enlargement and splenomegaly seem to be a little less frequent than in his series and other causes of splenomegaly must be excluded. Glandular enlargement has sometimes been so extensive as to suggest lymphoma, but this does not occur apart, as I have said, from cases misdiagnosed from the start.

Cervical Spine.—One of the more exclusive features of Still's disease is neck involvement (Ansell, 1964), producing limitation of movement mimicking ankylosing spondylitis and due, like the limitation in the latter, to involvement of the apophyseal joints of the spine resulting in fusion. The pathological process in these joints is the same as elsewhere, and is similar to that seen in adult rheumatoid arthritis, with synovial hyperplasia, fibrin incorporation, perivascular lymphocytes, and a lot of plasma cells, but because of the greater thickness of the cartilage, bone involvement and the subsequent radiologically visible changes are less common and longer deferred, which contributes I think to the rather better general prognosis.

Tendon Involvement.—This is sometimes seen and may be the only sign of the disease.

Terminal Finger Joint Involvement.—This is not uncommon, in contrast with adult rheumatoid arthritis where it occurs only rarely.

Pericarditis.—This is found clinically in perhaps 7 per cent. of cases, but is probably really rather more frequent (Lietman and Bywaters, 1963). It occurs only rarely before arthritis and is sometimes accompanied by pleuritis.

Eye Involvement.—This does not tie up closely with other features of the disease but is an important clinical feature, producing first of all keratitis punctata (Fig. 3); if iridocyclitis continues, deposits of calcium occur in the cornea, leading to band opacity (Fig. 4); adhesions, and later cataracts develop (quite apart from any cataract that may be

induced by steroid medication) (Smiley, May, and Bywaters, 1957; Smiley, 1960, 1965).

Sacro-iliac Joint Involvement.—This is seen in many patients, and we think it is of three different kinds:

- (i) An inflammatory erosion of a rheumatoid type without much radiological change;
- (ii) A sclerosing inflammation leading to ankylosis similar to that seen in spondylitis;
- (iii) A benign fusion of the two surfaces associated with severe hip disease (Bywaters and Ansell, 1965).

The incidence of these various manifestations is shown in Table IV.

TABLE IV
MANIFESTATIONS IN STILL'S DISEASE

Date	December, 1958		December, 1962	
Total No. of Cases	216		316	
Fever	96	44%	149	47%
Rash	43	19%	64	20%
Glands	74	34%	111	35%
Spleen	39	18%	62	19%
Liver	22	10%	33	10%
Eye	11	5%	26	8%
Pericarditis	9	4%	24	7%
Nodules	19	9%	23	7%

Amyloid Disease.—This is a very important complication seen in the more severe cases. Its most dangerous site is in the glomerular capillary walls, and it is usually detected by the development of proteinuria and leads to nephrotic syndrome with oedema and ultimately uraemia. In nearly 400 cases we have had sixteen (that is 4 per cent.) with amyloid disease—a number which will of course increase the longer we follow these cases. While we have shown that some of the signs of amyloid disease may resolve at least transiently (Parkins and Bywaters, 1959), it seems improbable that amyloid, once deposited, will undergo any real resorption, and our only hope for these patients is to stop deposition at a comparatively early stage, if we can, before uraemia and hypertension produce a terminal, irreversible state. We think it is permissible in such instances to try drugs such as chlorambucil, since this is one of the most inexorable complications that we meet.

Prognosis.—Other causes of death (Table V, overleaf) are due to infections of various sorts—some related to steroid therapy and some not.

However, as our 15-year follow-up survey showed,

TABLE V
CAUSES OF DEATH IN STILL'S DISEASE
400 cases followed for up to 20 yrs.

Renal Failure (Mostly amyloid—9)	..	..	..	..	..	11
Infection	Pneumonia	..	..	..	..	3
	Hepatitis	..	..	..	..	4
	Peritonitis	..	..	..	..	2
	Measles encephalitis	..	..	..	..	1
	Whooping cough (cerebral haemorrhage)	..	..	..	..	1
Anaemia	Refractory	..	..	..	..	1
	Pancytopenia	..	..	..	..	1
Accident	Fat embolism	..	..	..	..	1
	Post-operative (aortic stenosis)	..	..	..	..	1
"Still's" Disease	..	..	..	..	..	2
Total	..	..	..	..	..	28

the majority of our patients do well (Tables VI and VII).

TABLE VI
FUNCTIONAL STATUS GRADED 1 TO 5
RESULTS IN 1966 AFTER 15-YEAR FOLLOW UP

Sex	Male (55)						Female (85)					
	1	2	3	4	5	Dead	1	2	3	4	5	Dead
Initial	18	9	15	10	3	0	20	16	19	18	12	0
5 yrs	3	5	7	20	18	2	3	7	17	22	32	4
10 yrs	3	2	2	18	28	2	1	2	18	27	32	5
15 yrs	2	1	4	13	31	4	1	2	15	24	34	8

Of 140 patients we have followed for 15 years, 80 per cent. are living a fairly normal life, although one-third still have active arthritis controlled by anti-inflammatory agents. Some patients return to normal very quickly and others grumble along for 5 or 10 years before they become inactive (Fig. 5). My feeling, seeing such children as out-patients, growing up—a few from the 1940s and more from the 1950s—graduating on one side of the bed to high heels, lipstick, and mini-skirts and on the other to beards and jobs—is that while there are a

TABLE VII
CASES FOLLOWED FOR 15 YEARS FROM ONSET

Sex	Male	Female
Total No. of Cases	55	85
Dead	4 (Amyloidosis 1)	8 (Amyloidosis 3)
Available for Assessment	50	76
Active Arthritis	17 (34%)	21 (28%)
Iridocyclitis	3	8
{ chronic	4	0
{ acute	3	2
Amyloidosis	5	0
Ankylosing Spondylitis	0	2
Psoriasis	34/47	51/69
ESR less than 20 mm./hr	35/47	9/72
Positive DAT or Latex Test		
Married	12	29
No. of Children	14	32

few who can ultimately be categorized differently, the vast majority have a relatively benign disease entity similar to sero-negative rheumatoid arthritis of adults but usually of better prognosis (perhaps only because of their age), sometimes with rash—almost always sero-negative, and occasionally associated with ankylosing spondylitis in male relatives or sero-negative rheumatoid arthritis in female relatives (Ansell, Bywaters, and Lawrence, 1962).

Doctor John Lawrence, to whom we owe a great debt of gratitude for his participation in the family study of Still's disease and much more besides, is more willing than I am to be dogmatic on the relationship of Still's disease to ankylosing spondylitis. I am sure that the epidemiological approach is going to be a fruitful one, but in a comparatively rare disease (and we have shown by looking at our local cases a prevalence of 0.06 per cent. in school children over a 5-year period) this must be based on hospital-referred cases, and ultimately depends, therefore, on criteria adopted by the hospital for admission, by the

Fig. 5.—Chart showing course of Still's disease in a girl aged 4½ years at onset in 1948, followed by 7 years of intermittent disease activity. Now, 18 years later, she is well, married, and rearing a family, with only minimal radiological residua.

general practitioners for referring, and by the parents for taking the child to the general practitioner. The peculiar and arbitrary divorce between paediatrics and internal medicine also helps to make data based on this triple sieve difficult to interpret.

To summarize, then, chronic juvenile polyarthritis is a wide term: Still's disease is an historical term, and juvenile rheumatoid arthritis is an exact, but misleading, term. All such terms should be regarded as shorthand notations: reliance instead should be placed on criteria chosen by international agreement for a particular purpose,* as has been done for adult rheumatoid arthritis, and subsequently verified or confirmed by multicentre action. Only then shall we really know what we are talking about.

What then is Still's disease now as we have defined it? For the patient and his parents we can give some picture of what this means in terms of prognosis and the sort of care needed, based firstly on the average course followed to 15 years, and qualified by special features such as DAT, the number of joints involved, and the presence of erosions. For the economist we can say that, over a period of 5 years, Still's disease severe enough to refer to hospital is a rare disease, but one that may last a long time. For the scientist, we have no answer yet, but we believe that what we have defined as Still's disease or juvenile chronic polyarthritis on the basis of a hospital-referred group as part of a much larger one, may include a small number of difficult cases, including undeclared ankylosing spondylitis, undeclared psoriatic arthritis, or ulcerative colitis, and uncommonly, rheumatoid arthritis as in adults, but that the great bulk, whether monoarthritic or polyarthritic, comprises a relatively uniform and benign sero-negative group—having close similarities and familial links with the sero-negative rheumatoid arthritis of adults.

This, however, is an Oration and should enjoin universals from the particular. The only categorization of disease that I am sure will stand up to the test

of time is that every patient has his own disease and that the physician must understand and treat the individual's disorder in all its social, domestic, and familial ramifications: this is the art of medicine. As a corollary, a disease exists in time, and its time-characteristic (its course) is more important than those point-prevalent characteristics which are emphasized by textbooks. The science of medicine employs other more complicated categorizations to further our understanding of disease, but such groupings must remain tentative and mutable and subject in the long run to categorization by outcome. As Heberden wrote:

"It is necessary to be upon our guard against experience itself when delivered in a system . . . the best materials of natural knowledge are the plain facts themselves, just as they come from nature."

I realize that the average man or woman will eagerly grasp a framework of theory in preference to a handful of facts, but I am addressing a very much more than average audience, and I hope I have given you plain facts with that minimum of systematization that is necessary for presentation and understanding.

The grey hair of clinical experience conceals no doubt a great deal of unconscious codification, but, as every young man knows, this is firstly no substitute for conscious analysis and secondly it carries under the thatch innumerable possibilities of bias (as some would say, more warp than woof), as of course under any thatch. Experience is one thing: knowledge, that is the winnowed essence of experience, quite another. The ability to profit from experience and to turn mere impressions and numbers into meaningful associations (each with its appropriate test of significance) needs application, judgment, sophistication, dedication, and organization, as well as some rudimentary acquaintance with statistics, if not with a statistician. Then experience, something we can all boast of, becomes knowledge, which takes its rightful place in that grand edifice of accepted, still controvertible, but seldom controverted fact that we call science and to which William Heberden so signally contributed.

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