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Citation for final published version:

Latimer, Joanna Elizabeth, Featherstone, Katie , Atkinson, Paul Anthony , Clarke, Angus John , Pilz, Daniela T. and Shaw, Alison 2006. Rebirthing the clinic: the interaction of clinical judgment and genetic technology in the production of medical science. *Science technology & human values* 31 (5) , pp. 599-630. 10.1177/0162243906289613

Publishers page: <http://sth.sagepub.com/cgi/reprint/31/5/599>

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Rebirthing the clinic: the interaction of clinical judgement and genetic technology in the production of medical science.

Joanna Latimer, Katie Featherstone, Paul Atkinson, Angus Clarke (ESRC Centre for Economic and Social Aspects of Genomics, Cardiff University), Daniela Pilz (Department of Medical Genetics, School of Medicine, Cardiff University) and Alison Shaw (Brunel University).

Address for correspondence:

Dr JE Latimer

School of Social Sciences,

Cardiff University,

The Glamorgan Building,

King Edward V11 Avenue,

Cardiff, CF10 3WA.

United Kingdom.

e-mail:

Tel: 02920 876908

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Key words: clinical dysmorphology, genetic science, molecular technology, clinical classification, medical knowledge.

Abstract

We explore the relationship between science, technology and clinical process in the context of the new genetics through an examination of clinical work in the development of genetic science. In doing this we rethink the nature and location of knowledge-building in medical knowledge. Drawing on ethnographic research in clinical settings, we focus on the medical specialism of dysmorphology, which is the medical study of complex syndromes that impair physical development, often giving rise to abnormal appearances. Dysmorphology involves the professional recognition of distinctive physical features and the identification of a large number of named syndromes. Our findings indicate that dysmorphology represents a configuration of traditional clinical processes and new approaches to patient categorization using genetic profiling. But clinical work in dysmorphology is about much more than fitting patients into prefixed diagnostic categories. Rather, it emerges as crucial to the development of genetic classification, which is itself characterised by ambiguity, uncertainty and deferral. Specifically, we show that there are a number of clinic-based technologies and techniques that are, alongside molecular technology, involved in genetic categorising and the

building of classification in genetics. We examine these findings to suggest that the clinic in dysmorphology is reborn as a site involved the production as well as the reproduction of medical knowledge.

Introduction

We examine the interaction of clinical perception and molecular technology to reconsider the nature and location of science in the development of genetic technologies.

Specifically, we focus on the processes of genetic categorization within the clinical specialty of dysmorphology. Categories are the basis of systems of classification and are infrastructural to organisation (Douglas 1966); categorical work consists of distinguishing, naming and sorting things into kinds or classes (Bowker and Star 2000). Categories arise from ‘work and from other kinds of organised activity, including conflicts over meaning, that occur when multiple groups fight over the nature of a classificatory system and its categories’ (Bowker and Star 2000: 285). *Genetic* categorization is the specific work of distinguishing features and characteristics of persons (and other animals) as having (or not) a genetic origin. This work takes place within different domains, including the clinic and the laboratory and our analysis explores how genetic categorization is accomplished in the interaction of these two domains; although it is not necessary to describe the relationships in the agonistic terms employed by Bowker and Star.

By genetic categorization, we do not refer simply to processes of recognition (fitting people into extant categories). Rather, we refer to patterns of identifying and naming physical features and other effects in people and in families as having a *genetic* base. What emerges from genetic categorical work is the very conception of the genetic, as an emergent and provisional domain of classification. It is important to begin to understand how genetic categorization is accomplished because it has moral and personal consequences: for example, new categories for identity (e.g.

Brodwin 2002; Rabinow 1992, 2000; Strathern 1992, 1996); ‘genetic discrimination’ (Ettore 2002: 18); or the assessment of risk to future generations (Chadwick 1992). Our analysis focuses on the production of medical categories themselves (Yoxen 1982; Osbourne 1990), rather than on the impact of extra-medical social or cultural factors – a major strand in the sociology of medical work (e.g. Jeffery 1979, White 2002, Berg 1992, Dingwall and Murray 1989).

We draw on ethnographic research on the clinical specialism of *dysmorphology* to explore the work of genetic categorizing. Dysmorphology is the professional discipline of delineating disorders affecting the physical development of individuals, before or after birth (Aase 1990). Our observation of clinical process indicates that dysmorphology is an important case of the intersection of clinical perception, judgment and molecular technology (see also Shaw et al 2001). We begin by considering the genealogy of the clinic in respect of the relationship between clinical work, science and technology. We then go on to describe the different elements of dysmorphology clinical process, including the different techniques, technologies, materials and practices involved. In our analysis, genetic clinical process is characterized by the privileging of clinical expertise over other kinds of technology.

Clinical expertise, as in earlier accounts of medical practice, involves a very special form of medical perception or ‘gaze’, as a particular ability to say that one ‘sees’ (Foucault 1976) in a disciplined way. The performance of clinical expertise is accompanied by the expression of uncertainty, ambiguity and deferral over the attribution of a clinical diagnosis (cf. Bharadwaj 2002, Hedgecoe 2003, Sarangi and Clarke 2002). Rather than identifying these characteristics of clinical process as a failure of science and

technology, we address the significance of explicit ambivalence, uncertainty and deferral over genetic diagnosis.

We conclude that, in the current case of dysmorphology, clinical work does not just fit patients into extant diagnostic categories. Clinical work also involves identifying and naming *which* patterns of physical features and other effects have a genetic origin. Clinical work in dysmorphology constitutes 'categorical work' (Bowker and Star 2000) that is as much to do with the construction and refinement of categories as with their mere application. This finding is important because it prompts us to review how the dysmorphology clinic performs the relationship between science, technology and clinical work, which itself is of socio-cultural significance.

The Clinic

The genetics clinic offers scope for a contemporary micro-sociological understanding of the relationship between clinical work, science and technology, which discriminates between different sites and sources of technology and which more sharply focuses on the exercise of clinical perception and judgement as sources of genetic science. This is partly because the categorical work of sorting, identifying and naming patterns of physical features and other effects as having a genetic origin is still a relatively new specialty in medicine. However, it also reflects a much longer history of the interactions between clinical judgement and biological or biomedical science the pre-date the development of 'the new genetics' and its clinical applications.

Foucault (1976) suggests that the clinic was constituted as the new location for the discovery of positive knowledge about the body and disease. He examines how

medicine shifts from dyadic relations at the bedside, where the doctor observes the patient, and supports nature as illness runs its course, to the hospital, and the development of the clinical method, as a *systematic* method of observation and classification. For Foucault, the methods of the clinic constitute it as an important site of ‘human science’. It is not that the bedside was completely abandoned – to this day, dyadic relations between patient and doctor remain possible as an available source of information to contextualise medical understanding, but the clinic itself becomes the site of production. What is produced is both medical scientific method and medical knowledge. Important aspects of the clinical method include categorical work based on observation. Here observation has to be ‘pure’ and ‘uncluttered’, free of the chimera of prior theories. What are being observed are bodies - the surface of the body for signs, and the depths of the body for the ‘invisible’ causes of these signs. The ‘gaze’ as modes of perception and annunciation makes the invisible visible (cf. Long 1992). Critically, then, it is the clinic, not the laboratory, that is the locale for the discovery of modern medical knowledge.

The knowledge produced within the clinic was used to create anatomical maps of the body and classificatory systems of disease and its effects on/in the body. These methods are now recognizable as the traditions of clinical nosography and the classificatory mentality of medical thinking (King 1982). Alongside the clinical work of observation and categorization, knowledge and method became increasingly standardised and codified. Thus the possibility arises for clinicians to be (re)presented not as natural scientists, ‘listening, deciphering, interpreting’, but as disciplined subjects ‘looking according to a grid of perceptions, and noting according to a code’ (Foucault, 1991:56). Thus, the gaze of the clinician, exercised and disciplined in ways of seeing/saying, itself

becomes a technology. Through a correct and systematic reading of the body the signs and symptoms can be identified (or read) which are then 'recognised' as those of a particular diagnostic category (Atkinson 1997).

Thus, the methods of knowledge production developed in the clinic lie across two axes. The first axis allows the doctor-as-natural-scientist to move between methods of classification that read the surface of the body for signs, and technologies for making the inside of the body as the location of disease, visible. The second axis allows the doctor to move between the naturalist observation of the causes and effects of disease on/in the body, as modes of categorizing, and classificatory systems that fix medical science as 'grids and codes'. This duality in medical judgement is made more complex by the appearance of another site and source of science, the laboratory, and the development of new kinds of laboratory-based technologies, such as blood tests (cf. Atkinson 1995). Increasingly the rise of laboratory science *appears* to shift the locus of medical science from the clinic. Here the relationship between the clinic and science could be (re)presented in a similar way to the relation between the farm and the laboratory in Latour's study of the pasteurisation of France (1988) that is as 'remote control' (Cooper 1992). Within this view, the clinic is remote and not involved in the production of medical knowledge. Rather, the pressure is for clinical staff to apply knowledge determined elsewhere, to efface complexity and heterogeneity, and to make decisions and 'dispose' (Berg 1992, Latimer 1997) of patients, at an ever-increasing speed. Thus, the contemporary clinic could be reconstituted as a site of intervention in which science is merely consume and complete clinical episodes are produced. The point is not that grids and codes are abandoned within the clinic; instead, these are harnessed and sedimented

within classificatory systems determined elsewhere.

Representing the clinic as remote marginalises the importance of discretion and perception in clinical decision-making (Armstrong 2002). While the contemporary object of the clinical gaze is, increasingly, the relation between the observed body and the dispersed images of pathology, establishing this relation relies upon processes of collective reasoning and adjudication rather than the simple application of prescriptive schemata (Atkinson 1995). In addition, classificatory systems themselves can be understood to hide more than they reveal: they are reductions that efface the complexity and ‘messiness’ of medical categorising (Bowker and Star 2000).

Our discussion of knowledge practices in the clinic, and the intersection of genetic science and clinical judgment, intersects with several key debates. On the one hand, there is the general debate concerning the interactions of ‘the new genetics’ and clinical medicine. On the other hand, there is the more specific issue of the ‘geneticisation’ of clinical medicine and clinical entities. The two are themselves inter-related in key ways; our own ethnographic evidence relates to both of these areas of contention, although our detailed case study of dysmorphology clinics departs from the general formulation of both.

The relationships between clinical medicine and biological science have a long history of contestation. Jamous and Peloille (1970), for instance, document tensions between emergent laboratory science and the privileged status of clinical medicine in nineteenth-century France. Likewise, Atkinson, Reid and Sheldrake (1977) discuss boundary disputes within medicine over ‘indeterminate’ or tacit aspects of clinical judgment and ‘technical’ knowledge. Atkinson’s ethnography of practical work and talk

among haematologists (Atkinson 1995) demonstrates the micro-politics of medical knowledge, whereby the personalised authority of the clinician intersects with – and may over-rule – knowledge invoked on the basis of research and ‘journal science’ (cf. Fleck 1979). The historical and philosophical contribution of Canguilhem (1989) to our understanding of medical knowledge has been especially influential in this general area. Drawing on the history of physiology and pathology, especially in France, Canguilhem argues that the pathological is never reducible to the normal, and that the identification of clinical, pathological entities cannot be equated with the extension or extrapolation of the normal, either in terms of excess or in terms of deficiency. In general, he argues, one should not confuse the *qualitative* categories of the normal and the pathological with the quantitative expression of physiological values. From Canguilhem’s perspective, therefore, the pathological occupies a distinct domain of knowledge deriving from the clinic, and relatively autonomous from that of the laboratory. Similarly, Sinding (1989, 1990, 1991) has explored the relationships between clinical medicine and biological science in her interpretation of the trajectory of rickets as a clinical entity.

In recent years, the relationships between the ‘new genetics’ in medicine and the laboratory have received particularly close attention from this perspective. For instance, Keating and Cambrosio (2001) have demonstrated that historical accounts of the ‘new genetics’ have been markedly, and inaccurately, skewed: significant advances are attributed to basic sciences and laboratory work, while major contributions arising from clinical research and practice are marginalized or ignored. They conclude that even sociologically sophisticated narratives, like Fujimura’s genealogy of oncogene research (Fujimura 1996), imply a linear model of development whereby basic research impacts

upon clinical practice (cf. Gaudillière 1993). By contrast, Keating and Cambrosio conclude rhetorically: ‘Could we not say that in many respects clinical research and practice are constitutive of the new genetics and not some kind of passive receptacle awaiting impact?’ (p. 352). Similarly, Cambrosio, Guttman and Keating (1994) have examined the controversial and contested use of lymphocyte subset monitoring in transplantation therapy, concluding that research instruments can generate clinical diagnostic routines even where there is no consensus as to efficacy. Following Canguilhem, they suggest that practice may be informed by an unproven belief that ‘the monitoring of normal physiological variables will lead inevitably to the discovery of pathological signs’ (p. 539). Keating and Cambrosio (2003) have extended their reflections to develop their own model of ‘biomedical platforms’, which they understand to be new forms of knowledge that are grounded exclusively in neither the biological nor the clinical. They argue that their model provides a way of capturing the emergence of a new way of making knowledge in the period after World War II that transcends the divide between the normal and the pathological, creating new ‘truly biomedical entities’ that exist simultaneously as normal biological phenomena and pathological signs. They ground this analysis in their detailed consideration of the development of cell-surface markers. They themselves define ‘biomedical platforms as material and discursive arrangements that act as the bench upon which conventions concerning the biological or normal are connected with conventions concerning the medical or pathological’ (p. 332). This model also stresses the intersection of the laboratory, the clinic, industry and mechanisms of regulation in networks of interdependence.

The recurrent motif in this expanding research literature is a scepticism

concerning *reductionist* explanations of medical knowledge. There is a need to avoid the assumption that medical knowledge and practice can be accounted for in terms of increasing molecularization (e.g. de Chadarevian and Kamminger 1998) or the rise of technology (Wailoo 1997). This is also a feature of the second key debate with which our work engages – concerning the so-called *geneticization* of contemporary medicine. Kerr's exploration of cystic fibrosis is a key case in point (Kerr 2000). She demonstrates the flexibility of genes and disease entities in the complex intersections between genetic and clinical research. While genetic reductionism is a feature of much of the scientific and medical texts she examines, she argues for social-science analyses that 'contextualise genetic reductionism' (p. 870), stressing the 'variability and contingency' that characterises the accomplishment of genetic categorizations. The consequent dialogue between Kerr and Hedgecoe (Hedgecoe 2003, 2004; Kerr 2004) serves to underscore the fact that while social scientists may wish to treat 'geneticization' as a topic for inquiry (as reflected in the rhetoric and practices of scientists and clinicians), it should not be invoked as an unexamined *explanation* for current practice (see Hedgecoe 2002, Hedgecoe and Tutton 2002, Gibbon 2002). Cox and Starzomski (2004), discussing the construction of autosomal dominant polycystic kidney disease, also argue that the complexities of everyday practice escape simple characterizations as 'geneticization'. There are, of course, wider cultural analyses in which the notion of geneticization has been invoked to account for generic consequences of the new genetics (e.g. Lippman 1992, Finkler 2000) and to contest strong versions of a geneticised 'medicalisation' thesis (Cussins 1996, Lock and Kaufert 1998, Martin 1998).

There is, however, one major difference between the debates over geneticization

and biomedical knowledge we have just referred to and our own empirical work reported here. Authors such as Keating and Cambrosio base their analyses on the close historical reading of published texts, and on interview materials gathered from protagonists. Likewise, Kerr's analysis of cystic fibrosis is textual, based on a reading of published research and clinical work. Our own interest in the encounter between genetics and the clinic is grounded in a different research tradition. Our analysis is not based on the recent history of published science, but on the ethnographic exploration of mundane practices of genetic medicine. For us, the relationships between clinical and scientific knowledge are located in the interactions of specialists in the clinic. The respective contributions of laboratory science and clinical judgement are not, therefore, matters to be adjudicated or evaluated, but to be observed and interpreted within the ordinary, practical activities of diagnostic and related work. In that sense, therefore, the contribution of, say, Canguilhem (1989) is tangential to our own intentions. We are not concerned with questions of whether *in principle* the pathological can be derived from the normal or *vice versa*. Our sociological interests imply an indifference to Canguilhem's epistemological programme. As we shall see, our ethnography implies a transformation of Canguilhem's problematic. Rather than being a philosophical issue that requires a normative interpretation from observers, the relationship between laboratory science and clinical inference is a *practical* matter for the participants themselves. The evidential relationship between clinical observations, diagnostic inferences and laboratory investigations is a recurrent topic of everyday medical work itself. It is not susceptible to a general epistemological resolution. To that extent, our interests also diverge from those of Keating and Cambrosio (2003). They themselves propose a solution to the dichotomy between the normal and the

pathological by invoking biomedical or bioscientific entities as new forms of knowledge in their own right. However, their analysis, not directly grounded in clinical ethnographies, is as stipulative as Canguilhem's. In identifying biomedical platforms as the sites of new entities, they are in danger of pre-empting the analysis of how different varieties and sources of knowledge and expertise are invoked, shared, contested and interpreted in the conduct of clinical work.

Studying dysmorphology

In what follows, we analyse diagnostic processes in the clinic as mode(s) of perception and enunciation that allow clinical staff to see and name disease as having or not having a genetic origin. We are concerned with how participants use different kinds of evidence, including that produced by traditional clinical perception as well as evidence produced by harder technologies, such as molecular tests, as the basis for categorizing particular signs and effects *as* genetic. That is, we explore how genetic categorizing is accomplished and identify the role different technologies play in this work. Our focus therefore is on the different practices, materials and technologies involved in dysmorphology clinical process; we describe these and examine how they are draw on (or are excluded) in the work of categorising patients.

The analysis presented here part of a wider collaboration between social scientists and clinicians who are practitioners in the field of genetics. The examples drawn upon arise from a wider ethnographic study carried out in the clinical genetics service of a major UK teaching hospital. One aspect of the study involved the participant observation of two clinical genetics teams, including weekly team meetings (n= 52), home visits carried out

by the genetics specialist nurses (n=7) and clinical consultations (n=140). Our examples draw upon notes taken during and immediately following each period of observation and include near-verbatim text. In addition, a large number of less formal encounters between professionals was observed.

The work of categorizing patients within dysmorphology involves mapping patterns of physical features, particularly the face, in the individuals referred (who are mainly babies and children), and across families and patient populations. Such features may or may not be abnormal in themselves, however, particular patterns of physical features have come to be associated with underlying systemic abnormalities, such as heart defects and skeletal anomalies as well as delayed intellectual and social development. For example, Down Syndrome and Marfan Syndrome, which both have distinctive patterns of physical features. Down syndrome includes a very distinctive face, with pointed incurving little fingers, short stature and learning difficulties, while Marfan syndrome also has a distinctive face, with tall stature, long slender limbs, joint laxity, and eye and cardiovascular problems.

Dysmorphology classification involves the presence of clusters of associated features and symptoms. When these patterns are deemed to have reached a sufficient level of regularity across different cases to establish that a common pathogenic mechanism is operating, they are named as a *syndrome*. Many syndromes are very much ‘in the making’.

A genetic basis is attributed to the majority of these syndromes. The two main genetic bases are categorised as single gene defects and chromosomal abnormalities. The precise genetic basis for a particular syndrome or a particular case is important because

different bases present different risk implications for family members. Where the latter is identified as the cause of the condition, there is a low level of risk of recurrence in the family.

For the clinician, the pattern of the clinical features is referred to as the phenotype and there is often some variability in how the phenotype appears across different individuals with the same syndrome. The phenotype may imply an underlying genetic base, or genotypes. While there are several thousand documented syndromes within international clinical databases and textbooks, only a small number have definitive genetic tests.

The organisation and division of genetic work

In the service under study, genetic work is distributed between consultants of clinical genetics, genetic specialist nurses (GSNs), other genetic associates, such as genetic counsellors, trainees in clinical genetics (specialist registrars or SpRs), other clinicians (GPs and other clinical specialists) and the family. In the current service, clinical genetic process is also distributed across different occasions: the home visit, the clinical consultation and the regular team meetings. These occasions are now described.

After referral, but prior to most clinic appointments, the genetic specialist nurse or counsellor makes contact with the individual referred (the proband) and their family. Some families receive a home visit prior to their clinic appointment. The purpose of this visit is to take a history, create a family tree, and collect relevant materials (e.g. photographs). In addition, the nurse obtains permission to trace and acquire medical records for relevant family members, including test results and autopsy reports. At this

stage there is no examination of the proband. A report of this visit, including the family tree, is placed in the medical records held by the clinical genetic service.

Usually, both the consultant and the GSN who has conducted the home visit are present at the initial clinical consultation. Here, the consultant discusses the route of referral and the family tree, and takes a history. At this stage a physical examination of the proband is carried out and the consultant may take photographs of those features that appear distinctive. Potential diagnoses, tests and other materials that may be required to aid a diagnosis are discussed, as are (if known) the causes of the condition, its progression and the risk of recurrence.

Team meetings usually consist of all members of the clinical team working under the direction of the genetic consultant. The relevant consultant geneticist together with the SpR and one or two GSNs were present at the team meetings observed in the study. Within these meetings members review and prioritise new referrals, construct a diagnosis for both new and ongoing cases, gather materials to aid diagnosis and organise future clinics. These different materials are now discussed.

Genetic diagnostic practice and technology

As well as all the usual clinical technologies and processes, such as clinical history, biochemistry and CT scans, there are three distinctive materials used in dysmorphology diagnosis: photographs, family trees, and molecular and cytogenetic tests. These are now described.

The clinical team uses two types of photograph: slides taken during the clinical consultation and family photographs collected by the GSN at the initial home visit.

Photographs taken in the clinic are used to make a record of specific and '*unusual*' features, such as a unusual hands and feet or a '*distinctive*' face. Family photographs are used to trace specific features, either in the proband themselves or across other family members. Some of these photographs are filed in the medical records and it is these rather than the patients themselves who are circulated at clinical meetings of experts at regional, national and international levels for teaching, research and diagnostic purposes (see also Featherstone et al forthcoming; Shaw et al 2003).

The family tree is initially composed by the GSN during the home visit. The family tree is also called a pedigree; the metaphor associates the family tree with notions of breeding. The GSN asks family members to provide information about their blood relations and their relations by marriage across three generations. Each member of the kindred is represented by a symbol to indicate their gender and latent or manifest disease status if known, along with details of their name, age, pregnancy history, health status and any other potentially relevant information. The tree may be modified at the clinical consultation.

The construction of a family tree allows the clinical team to map similarities in features across family members. Through a process of inscription the family tree marks these features as possibly familial. The family tree then takes on its own life: its constructed nature is effaced and it is, like other clinical materials, placed in the proband's medical records as one form of representation of the family.

Clinical genetics thus draws upon several clinic-based technologies in the work of categorizing patients. Photographs and family trees help us understand something about how patients are categorized because they are the material effects of clinical genetic

knowledge practices. Dysmorphology also draws upon various techniques of molecular analysis. However, even though most dysmorphic syndromes are thought to involve submicroscopic changes in DNA sequence; for many syndromes there are no tests. As we will show, even though genetic tests are used in the clinical work of genetic categorization, they do not necessarily determine it.

In the rest of the paper, we focus on the team meetings as a key site where the different materials produced by each aspect of the clinical process are assembled, interpreted or dispatched in the work of genetic categorizing.

‘Keeping people on’

Securing a genetic diagnosis may be a protracted process, a matter of years of investigation and observation. In the following extract, the clinical team (the GSNs, SpRs and the Consultant Geneticist) are sitting together at one of their weekly meetings in the department of medical genetics. They are discussing a young boy, Simon, a ‘follow-up’:

GSN1: A follow-up. He’s a dysmorphic chap we’ve looked at together, he’s not Smith-Magenis...He’s obese with ADHD [attention deficit hyperactivity disorder] and difficult behaviour, no significant dysmorphic features, I thought about seeing him in a year.

Consultant 1: How old?

GSN1: Eight.

SpR: [Looking at photographs] He’s big.

Consultant 1: I remember his photos, leave it more than one, maybe two years. I

wouldn't discharge him. He's got a lot of problems, it's worth keeping people on. The key aspect that we want to emphasise here is the idea of '*keeping people on*'. In the absence of a diagnosis, the clinicians are still working to categorize Simon; he is dysmorphic and has many associated problems. As a follow-up, he has been seen before, however, although the Consultant cannot categorize his problems within a specific syndrome, he still wants to keep him within the clinic and see him in a few years time. Thus, the work of '*keeping people on*' is as important as the work of making a diagnosis. This observation contrasts with other studies of medical processes that suggest that clinical work is usually aimed at achieving decisions that lead to the *disposal* of patients (Berg 1992, Latimer 1997).

Our observations of the dysmorphology clinic suggest, therefore, that legitimating deferral is as important as making a diagnostic decision. Sometimes deferral is needed because the patient is a baby, and signs may emerge as the child gets older. However, Simon is eight years old, and although he does not fit any recognised syndrome, this may change.

Diagnostic decisions, or the decision to defer a judgment, have to be legitimated, and we will examine the significance of such acts in this context. We now discuss the different ways in which deferral and decision are accomplished.

Looking for dysmorphia

Making a diagnosis or keeping a patient within the clinic in the absence of a firm diagnosis can be achieved by establishing that they are *dysmorphic*. Thus, an important starting point for the clinical team prior to seeing a patients in the clinic is the

examination of photographs during the team meeting. These are passed around and each look for distinctive physical signs and indicators on the body of the proband or their kin. An individual has to look dysmorphic, and the clinical team has to be able to see this look. However, fitting someone's features into a classification of dysmorphia is not self-evident; it has to be established. For example, in the following extract the team discuss Louise,

GSN1: Small jaw, cleft, heart defect.

[They discuss the referral letter and the term dysmorphia, the consultant turns to the researcher]

Consultant 2: Have you heard of the term FLK?

Researcher: Yes, 'funny looking kid'.

Consultant 2: It means a few dysmorphic features, I think its better to say that they look slightly different, funny, a bit odd looking, than to say dysmorphic.

Thus in looking for dysmorphia an individual's features have to be shown to be different or '*odd*' in some way. Distinctiveness is established as the team offers their observations of how a patient looks. In the following extract, the team are examining photographs of Sam:

GSN 2: A follow-up. [Adds that she and the SpR had seen Sam previously at the clinic.]

SpR: Not particularly dysmorphic.

Consultant 1: Coarse looking though.

Although the SpR describes Sam as '*not particularly dysmorphic*', the consultant notes that he is '*coarse looking*' and this subtle distinction helps keep Sam within the realm of

dysmorphology. Thus, there are grades of dysmorphia. A common question raised by the team while looking at the photographs is whether a patient looks dysmorphic enough.

Consider the following discussion about Charles:

GSN 1: Yes, he's the new one to be seen, query Sotos. [She brings out two family photographs from her file. The first is of a young man in his late teens standing in a bathroom doorway with a towel wrapped around his waist - it looks as though he has just got out of the bath. In the second photograph he is sitting with his twin sister in either a restaurant or a bar, they are both smiling into the camera. The photographs are passed around and examined by all the members of the team.] He's got learning difficulties.

GSN2 : [Looking at photos] They're [his features] not striking. There were no complications during his birth.

Consultant 1: [He places the photographs back in the envelope and reads from the notes, commenting that his birth-weight was low even for a twin. The consultant then takes the photographs out of the envelope again, scrutinises them and passes them to the SPR.] I'm hopeless at talking about what I see, he has got a high forehead - but [gesturing to Charles's eyes] they're not down-slanting.

GSN 2: Apart from his forehead he doesn't look dysmorphic enough.

Consultant 1: But the forehead is quite striking.

GSN1: His CT was normal.

[They go on to speculate about other possible genetic origins to Charles' problems].

As the various members of the team scrutinise the photographs, they are considering

whether Charles does or does not fit a diagnostic category, Soto's syndrome. Their gaze is contextualised by GSN1, who points out that Charles has learning difficulties. GSN2 sums up Charles' look, stating that his features are '*not striking*', but maintains ambiguity over Charles' diagnosis by reminding the team that his learning difficulties were not caused by complications at birth (e.g. anoxia). Consultant 1 hesitates, suggesting that Charles' birth-weight was too low for him to have Soto's syndrome. As he puts the photographs away he seems to be about to dispose of Charles, relegating him, as it were, to the realm of normality; but in drawing the photographs back out of the envelope, he draws Charles back into the clinic.

The Consultant legitimates his action by stating that it is his inability to articulate what he sees, rather than the absence of something to see, that is the problem. Even though GSN2 suggests that Charles just '*doesn't look dysmorphic enough*', Consultant 1 persists by stating that the forehead is '*quite striking*'. GSN2 appears to reinforce GSN1's pressure to move Charles out of the clinic by saying his CT scan was normal. However, the ambiguity and undecideability over whether Charles is dysmorphic enough, together with his learning difficulties, is enough to keep Charles on in the clinic and the team continues the search for other genetic possibilities for categorizing Charles.

Seeing a Syndrome

As we have begun to identify, dysmorphology relies upon the traditional clinical skill of reading the surface of the body for manifest and/or latent signs or features. For dysmorphic features to suggest an underlying syndrome, it is not necessarily because they are abnormal in themselves. Rather, for a feature to signify the possibility of a genetic

syndrome it has to be aligned with other features across different anatomical systems. Thus the origins of pathologies begin to be made visible through the application of a disciplined gaze (Foucault 1976), even in the absence of definitive categories. This is made explicit in the consultant's comment about Charles: it is articulating what he sees and fitting these subtle signs within a particular syndrome that is difficult. The categories are still in the making.

In the extract above Louise's '*small jaw*' becomes significant in the context of other observations, a cleft palate and a heart defect. Similarly, Charles' '*striking*' forehead, when aligned with his learning difficulties, suggests a genetic origin, even though the nurses do not consider that he looks sufficiently dysmorphic. Thus, the molecular level can be 'seen' by being read into the various traces across different systems. The signs across different systems (long limbs, low brow, down-slanting eyes, pointy chin, hearing difficulties, etc) can be made visible as abnormalities because there are the beginnings of a map (however incomplete) with which to trace and link them. Thus, the genetic significance of any distinctive feature is constituted by the presence of other signs across different systems.

Even when one feature is defined as dysmorphic, this description is still indeterminate. Fixing a patient within a categorization depends upon the skill/craft of the clinical team to see other effects in a patient's history which are either associated with a known syndrome or which seem 'syndromic', that is, suggestive of a syndrome. For example, in the extract below, the team describes a referral, a young woman, Fiona, with a 'pointy chin':

Consultant 2: 16 [years old].

GSN2: What is it?

Consultant 2: Slightly unusual face, pointy chin, didn't identify a syndrome, learning difficulties, not major though, she's had facial surgery.

Even though her features do not fit neatly into any established category Fiona's physical features in conjunction with the evidence that she has learning difficulties, is enough to keep her within the clinic.

Seeing a patient as potentially syndromic is thus a matter of associating and aligning a patient's '*unusual*' visible features with other their problems such as '*learning difficulties*'. The features partly take on their significance as dysmorphic because they are unusual in themselves, and partly through their association with other problems. At this stage there is also the requirement, as we have already seen in the discussion about Charles, to differentiate between genetic and other possible origins of dysmorphia and learning difficulties, such as anoxia at birth or fetal alcohol syndrome.

The genetic basis of features still has to be accomplished and be made visible. Here it is important to differentiate between demonstrating that the patient's features are familial or indicative of a syndrome, that is, having a genetic base but non-familial, that is, not inherited. The first relies on the old clinical skill of seeing patterns of inheritance across generations, the second entails a stronger claim about aetiology that requires additional molecular, or other, proof.

Making it familial

Making it familial relies on the old clinical skill of seeing patterns of inheritance across generations. To do this, the clinical team draw together three strands of clinical (not

laboratory-based) evidence, the family tree, the family history, and family photographs. Seeing features and other effects, such as learning difficulties ‘in the family’ helps strengthen the evidence that the patient’s features are genetic. However, not all inherited features or traits are the effects of an underlying syndrome and part of the clinical work is to distinguish between what is familial, and what is (possibly) syndromic.

Where photographic evidence is available the physical features of family members are examined, discussed and compared. In the following extract, the team discusses Anna, a new referral, and her family:

GSN2: [From her file GSN2 brings out a small laminated professional school photograph of Anna as a young girl. In the photograph with her are her three younger siblings in a row, arranged in age order - eldest to youngest. She passes this to Consultant 1, who studies it closely.] They all need to be seen in clinic [she reels off a list of developmental and behavioural problems that the children have]. Three have learning difficulties, one attends a special school.

Consultant 1: [After studying the photograph for some time] Two have ‘big heads’ [He points this out to the researcher].

GSN2: They had CT scans, which failed to show anything up.

[They all agree that they need to start by looking at Anna.]

In discussing the case of Anna, the team traces features such as ‘*big heads*’ and learning difficulties across family members. They do this through aligning observations drawn from inspection of the photographs with specific details from the histories of family members.

Family photographs and family histories allow the team to look for features across

family members. In the clinic, the search for familial resemblances is pursued explicitly in the construction of a family tree (cf Bouquet 1994, Gibbon 2002, Nukaga and Cambrosio 1997). The following extract in which Lee is discussed illustrates how the family tree can be used:

Consultant 1: [He looks at photographs of Lee] I'd wondered about Smith-Magenis.. but there's nothing very striking to look at...he's a bit square-ish in the face.

SPR: Why has it come to light?

Consultant 1: [Examines Lee's family tree] The mother's sister's son has learning difficulties, maybe I should see him?

The Consultant states he can see nothing very striking when looking at Lee's photographs, however, after examining the family tree, he aligns information from this source (that the mother's sister's son has learning difficulties) with the fact that Lee's face is '*a bit square-ish*'. This alignment of evidence of a particular facial 'look' with a familial trace of a related problem is enough to strengthen the case for keeping Lee within the genetics clinic, even though his features do not look '*very striking*'. The Consultant draws on the family tree to imply that he can see something in the family that might mean that Lee's problems are inherited and potentially genetic. Thus, the idea that features suggestive of a genetic syndrome may be expressed across family members is also incorporated into the family tree.

So far, we have seen how the team aligns evidence that a patient's features may have a genetic origin. They draw together details not just from looking at a patient, but also from a patient's history, by examining photographs of the patient and their family,

considering the histories of the individuals within the family and the family tree, and offer observations of family members.

Making it genetic

We have noted how clinical process in dysmorphology is marked by deferral and undecideability. However, in assembling clinical data the team do sometimes stabilise a diagnosis.

The status of molecular tests is ambiguous. Definitive genetic tests are only available for a limited range of syndromes, and even when they are used, the clinical team may draw upon other evidence that can cast doubt on the reliability of a genetic test result. The clinical team move between their readings of the phenotype (physical features), and representations of the genotype (the molecular tests) in ways that privilege ‘the clinical picture’ rather than the laboratory based technology. The adequacy of the test may be regarded as insufficient to confirm a clinical diagnosis. However, rather than rejecting the diagnosis and disposing of the patient, the diagnosis may remain provisional. Casting doubt on the test occurs in a number of ways.

For example, a consultant and a GSN discuss the case of a family, the Smiths, who may have a genetic syndrome known as Fragile X. It emerged from their discussion that the results from the molecular test were unclear because they (the laboratory) ‘*couldn’t do a Southern blot*’. However, the distinguishing features of Fragile X could be traced in the family, the GSN states that the mother ‘*appears to have some learning difficulties*’ and that ‘*there are affected nieces and nephews*’.

In this case, although the genetic test results were unclear, other materials were brought in to support a diagnosis of Fragile X; information in the family tree and observations from the home visit indicate that the family may have the genetic syndrome, reinforce the provisional diagnosis. In this way a negative test result does not rule out a provisional clinical diagnosis where other evidence can be brought into play, such as family history. Thus the team assemble the evidence in ways that suggest that it is a genetic code that is being expressed, even if that code has not yet been mapped and cannot yet be ‘seen’ using molecular testing. Similarly, in the case of Alan, the blood test is negative but the clinical picture is strongly indicative:

Consultant 1: Myotonic dystrophy. Grip problems, cataracts, frontal balding.

GSN1: The full house almost but the bloods were negative.

Here the Consultant aligns the clinical evidence (grip problems, cataracts and frontal balding) to support the diagnosis of myotonic dystrophy, this man has the ‘*full house*’ even though the ‘*bloods were negative*’. The implication is that DNA mutational analysis was unable to detect the molecular change associated with the syndrome, however, the team believe it is there, they can ‘see’ the evidence of the genetic condition in the patient.

A negative molecular test result can sometimes lead to discharge; however, it is not enough in itself, but only when it can be aligned with other evidence. For example, in the case of Lindsay:

GSN2: [She describes a child who has mild dysmorphic features] But he looks OK on these. [She hands round two family photographs to the rest of the team.]

Consultant 1: There’s nothing, Fragile X and chromosomes have been done, the results are OK.

SPR: [Looking at photographs] Ooh! [indicating she finds the baby attractive]

Consultant 1: He's not very dysmorphic.

GSN2: [She agrees and adds] The child's father had retinitis pigmentosa 6 years ago. I checked with the mother if the child had any problems, but she's got enough on her plate.

The clinical team does not see the child's features as being dysmorphic and these observations confirm the negative test result, which like the photographs are also 'OK'. This information is also interpreted in the context of the family; the nurse suggests that it may not be appropriate to pursue a diagnosis because the child's mother has '*enough on her plate*'. Thus, the team moves away from a genetic diagnosis and Lindsay is discharged from the clinic.

It appears from the analysis so far that where a patient does not fit neatly into a clinical category this does not mean that they are discharged from the clinic. On the contrary, the clinical picture can be assembled in ways that legitimate deferral, so that a patient is 'kept on'. We have also seen that the molecular evidence itself is not necessarily relied upon. On the contrary, where there is negative molecular evidence but the team believes the clinical picture of a possible genetic disorder to be strong, a diagnosis is not excluded, but will remain provisional.

Stabilising dysmorphology diagnosis

As we have seen, where molecular tests are used, they are not privileged in any way as a form of evidence. Rather, we have seen how the clinical team move between different forms of evidence in their assessment of any particular case. Critically, the significance

of any particular aspect of the evidence (e.g. looking dysmorphic) has to be established through aligning the evidence. It is the judgement and skill of the clinical team in making a case for the clinical picture that appears to be privileged over any single technology.

What has emerged, however, is how in the field of dysmorphology it is difficult to give a definitive genetic diagnosis. These difficulties are amplified by something about genetic categorisation itself. While a tentative, working diagnosis is usually dependent upon the recognition of a pattern of abnormalities, a large number of syndromes share many abnormalities. In addition, there may also be a wide variability in how an abnormality is expressed (the phenotype) across different individuals with the same syndrome. The shared nature of many abnormalities, such as learning disability, together with the huge variation in phenotype, creates both opportunities and constraints on the clinical team. This complexity can increase the need for judgement and perception, for example:

Consultant 2: I've done some research on these three [he points to a pile of files for 3 children with dysmorphic features] there are 40 possibles [diagnostic categories] for this one, 50 for the other and 38 for that [He has fed their patterns of abnormalities into a dysmorphology database].

However, the overlap between syndromes and variation across phenotypes also creates opportunities for ambiguity. For example, in the following extract the clinical team once again discuss the young boy, Lee:

Consultant 1: [He gets out two photographs from the file, examines them and passes them to the SPR.]

GSN2: In the photograph I couldn't take from the family [at the home visit] he looks different.

Consultant 1: Thin upper lip.

GSN2: We've seen part of the family before, the father had RP [Retinitis Pigmentosa]

SPR: Are you thinking more Smith-Magenis than Prader-Willi?

Consultant 1: More Smith-Magenis

SPR: No, but not very Smith-Magenis either.

Consultant 1: These phenotypes are getting more elastic.

Thus, Lee remains on the perimeter of two different syndromes, because, as the consultant notes, to fix the configuration of abnormalities within one syndrome is difficult, these classifications are subject to change 'these *phenotypes are getting more elastic*'. This ambiguity creates the opportunity for Lee to be held within the genetic ground.

Further opportunity is created by overlap and variation; where the clinical picture does not fit one syndrome, another can be tried. For example, Kyle has been considered for a number of diagnoses since referral to the team:

Consultant 1: Someone who I think has Costello's. Originally he was query Noonan's, he does have some Noonan's features, Costello's is similar. [Adds that he had shown the photographs to two colleagues but they were non-committal].

GSN1: The child has major feeding problems.

Consultant 1: I'll tout them [the photos] round again.

No diagnosis had been confirmed for Kyle, although Noonan's had been suspected.

However, Costello's is '*similar*' to Noonan's and the child may fit this classification. Further, the discovery of '*major feeding problems*' renews the team's interest and this may be the additional information the team need to firm up a diagnosis because major feeding problems can signify neuro-developmental behavioural problems. The Consultant decides to keep Kyle on and '*tout the photographs around again*' at meetings with other experts.

The clinic, science and technology

The distinct nature of dysmorphology classification can be found in the way it explicitly uses clinical uncertainty as well as ambiguity and deferral. While it is increasingly possible to identify specific genetic tests for a number of dysmorphic syndromes that could previously be describable only in clinical terms, there is not a linear progression from clinical perception to laboratory testing.

Clinical perception and judgement, and the discretion of key experts that is differentiated as at the top of the hierarchy of knowledge practices in the work of categorising a patient and their troubles as possibly genetic or not.

What is being displayed is a degree of expertise: the 'gaze' has to be knowing and the clinician has to account for his/her perception or uncertainty. However, a definitive diagnosis for many patients cannot be accomplished at present. As one geneticist explained, even though the possibilities for delineating the precise molecular or chromosomal cause of a patient's problems by chromosomal analysis and differentiation are increasing, there is an ongoing process of clinical sub-and re-classification. Specifically, for any one disorder, there is often a progression from clinical recognition as

a distinct diagnostic entity, through the finding of the genetic basis of the disorder and the development of a diagnostic test, to a forced reclassification of the clinical entity to incorporate knowledge arising from the intersection of clinical and laboratory assessments. This is particularly true of anomalous categories of (1) clinical cases with no molecular changes found and (2) cases with the same molecular changes but a different set of clinical features, or none at all.

There are therefore several crucial features of the relationship between the laboratory science and clinical judgement in the context of dysmorphology. First, there is the progressive nature of the molecular laboratory based science, which is gradually introducing diagnostic certainty and an accurate understanding of disease mechanisms into this branch of medicine. The area of uncertainty is being steadily rolled back, but this process is only possible because of the prior clinical categorical work that allows laboratory science to tackle specific, soluble puzzles. Secondly, the advances of the laboratory science then permits a further refinement of the clinical classification of those cases and entities for which no precise understanding has yet been achieved - an iterative, reflexive and self-referential process. Finally, where a precise diagnosis is not achieved, clinical judgement is important in deciding whether a genetic basis is *likely* to be attainable in the medium future - whether future clinical genetic assessments are likely to be worthwhile. Thus in dysmorphology there is dependence on the clinic as well as the laboratory as a site of exploration and discovery in respect of the construction and refinement of genetic categorisation.

Conclusion

We have explored how clinical work in dysmorphology is involved in genetic categorizing, with a focus on the epistemological rather than the moral implications of genetic categorizing. Specifically, the paper has explored the interaction between molecular science, technology and clinical work within this speciality at the level of the clinic. The dysmorphology clinic is not simply a site in which some of the messy work of clinical classification is still observable, prior to its sedimentation in the 'pure space' of classificatory systems (Bowker and Star 2000). There is a need to examine carefully what 'the mess' of classificatory work signifies. We suggest that we are witnessing the 'rebirth' of the clinic as a site of production of medical knowledge; or rather, the continuous 'renaissance' of the clinic, in the repeatedly renewed intersections of the clinical and the laboratory.

At the professional team meetings, deciding upon the appropriate description and classification of individual cases does not entail a straightforward application of a predefined set of clinical parameters. As we have seen, team members examine and debate the clinical details, including photographs of individuals and family trees, and they try to establish a diagnosis, or alternatively to come to a collective decision that there is currently no diagnosis to be made. In this clinical domain, however, members do not simply discharge the patient who fails to fit into a specific diagnostic category. On the contrary, clinicians go to great lengths to legitimate keeping patients on. They do this where they can construct a case for the genetic basis of a patient's features of problems, even if that basis cannot yet be 'proven', that is, seen at a molecular or cytogenic level.

We have seen that clinical staff assemble and align how a patient 'looks' with their history or with evidence of traits or features across family members. A number of

clinic-based technologies are implicated in the work of genetic profiling.

It might be thought that the work of molecular scientists would progressively eliminate the function of clinical judgement and perception in this process of diagnosis and classification. To a limited extent, the laboratory science does help to provide definitive classifications, however, the relationship between science and judgement is not simply a unilinear one. Firstly, there may not always be genetic tests to support a diagnosis, or the sensitivity of the available tests may be limited. Secondly, cases classified as having equivalent clinical presentations may turn out to have different molecular bases (i.e. there may be genetic heterogeneity). Third, where genetic tests are used, clinicians do not necessarily throw the full weight of proof onto the laboratory findings. For example, negative results in one specific test in a typical case do not necessarily exclude a diagnosis. Here clinicians may throw doubt on the adequacy of the laboratory tests themselves. In many ways then, molecular tests themselves call for more clinical interpretation, rather than less.

Thus, within the field of dysmorphology, molecular tests are just one of many technologies that are assembled in the work of genetic categorizing. We have seen how molecular tests neither determine clinical process nor necessarily resolve diagnostic 'puzzles'. Indeed, sometimes, as we saw in the case of Adam, test results themselves are disposed of in order to keep a patient within the genetic ground.

This relationship between the clinic and the laboratory constitutes a reversion, at one level, to an earlier relation between science, practice and technology, one that performs human perception and practical expertise as essential to the progress of knowledge about the human body and its troubles. But of course it is not ever that

simple. For example, what is particularly interesting is how difficult it is to actually accomplish a definitive genetic diagnosis: genetic categorising is far from straightforward. Rather than contemporary forms of medical disposal and decision-making, in which the display of expertise entails speedy closure, what are found in the genetic clinic are *explicit* undecideability, uncertainty and instability over genetic diagnostic categories. We would like to (tentatively) suggest that undecideability, uncertainty and instability of genetic diagnoses as a prominent feature of dysmorphology clinical practice is highly significant and requires explanation when it runs alongside a firm commitment to a future of diagnostic certainty. Indeed it is the ambiguity and uncertainty which helps accomplish the need for that future, a future in which technology and classification will continue to press back the boundaries of the genomic unknown. Here we need to elaborate.

In our analysis of the genetics clinic rather than simply applying predetermined ‘grids and codes’ to make the face or the family ‘legible’ (Atkinson 1995), the lexicon of genetics is still very much performed as *in the making*. We want to suggest, therefore that undecideability and instability in genetic diagnosis helps perform clinical perception and judgement as important in *the generation* of medical knowledge. This is not to assert for a moment that we are witnessing in the genetics clinic anything new: Clinicians, as we have seen, are engaged in making the genetic basis of someone’s troubles explicit, or visible, in ways which involve familiar medical repertoires. They make the invisible visible through looking and deciphering: they look at faces, and across families, and display and interpret representations of faces and families, such as photographs and family trees. In addition they are engaged in an old reduction: via the use of molecular

technology the complexity of family and inheritance, and of all the traits and troubles that run across people's lives and bodies are reduced to a single (if sometimes complex) cause, the genotype. This methodology is nothing new in itself. Paradigmatically there is no gestalt switch (Kuhn 1970). But it is important for two reasons.

First, contemporary medical policy and practice performs the clinic as remote, as a space in which *scientific work* is no longer necessary. Rather science is increasingly configured as something that is merely being *applied* by clinical staff in the delivery of a service. In this representation of medicine, it is not the clinic but other centres of calculation that produce the science, fixed in the moment of a discovery, and diagnostic categories themselves are 'black-boxed' (Latour 1987). Second, in keeping people on, and by making ambiguity and uncertainty explicit, the dysmorphology clinic paradoxically maintains a commitment to a future of diagnostic certainty. The future is where molecular science (mapping the genotype) having worked alongside the clinical categorising of the phenotype helps to fix diagnostic certainty. Indeed, the combination of deferral, ambiguity and uncertainty mean that the clinic is helping to *legitimate* the need for more molecular technology, more molecular science. This is because it is only the 'objective' evidence of a genotype at a molecular level that can be treated as finally fixing a diagnosis, until that moment diagnosis remains provisional, a matter of opinion. Thus in our study the dysmorphology clinic emerges as a site in which some of the messy work of clinical classification is still observable, prior to its standardisation in classificatory systems, at the same time as it performs a commitment to a future of positive knowledge of genetic facts. It is this paradox which means that the genetics clinic is reborn as a site of discovery involved in the production of new knowledge, new

categories, but as those become fixed it may of course see its own demise.

Acknowledgements

We are grateful to all the staff and patients who have participated in our research on dysmorphology, genetics and the clinic. We are also grateful to Aditya Bharadwaj, and to the anonymous reviewers for this journal for their constructive and insightful comments on earlier drafts. We gratefully acknowledge the support of the Wellcome Trust (award no.xxxx), and the Economic and Social Research Council (award no. xxxx) for their financial support for the studies on which this paper is based.

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